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Effects of Chlorpromazine in Psychiatric Disorders. By IRVIN M. COHEN, M.D. 355

Chlorpromazine in the Treatment of Acute Alcoholism. By EARL H. MITCHELL, M.D. 363

Multivalvular Involvement in Rheumatic Heart Disease with Particular Reference to Cardiac Surgery. By JACQUES B. WALLACH, M. D., LESLIE LUKASH, M. D., and ALFRED A. ANGRIST, M.D. 368

The Fibrinogen Polymerization Test in Active Rheumatic Disease. By SAMUEL LOSNER, M.D., and BRUNO W. VOLK, M.D. 371

The Value of Parenteral Reserpine in Acute Hypertension. By FRANK A. FINNERTY, JR., M.D., and JAMES G. SITES, M.D. 379

The Possible Therapeutic Value of Cholecystectomy in Adams-Stokes Disease. By GEORGE A. MCLEMORE, JR., M.D., and SAMUEL A. LEVINE, M.D. 386

The Effects of an Adrenergic Blocking Agent, Regitine, Upon the Glucose Tolerance Curve in Peptic Ulcer Patients. By MARGARET HAY EDWARDS, M.D., and THOMAS K. RATHMELL, M.D. 392

Esterase and Lipase Activity of Leukocytes and Erythrocytes in Health and Disease. By E. BARTON HARDIN, M.D., WILLIAM N. VALENTINE, M.D., JAMES H. FOLLETTE, M.D., and JOHN S. LAWRENCE, M.D. 397

Acquired Agammaglobulinemia with Hypersplenism. A Case Report. By ROBERT J. ROHN, M.D., ROY H. BEHNKE, M.D., and WILLIAM H. BOND, M.D. 406

Clinical Pathological Conference. By HERMAN W. OSTRUM, M.D., PAUL GYORGY, M.D., and JEROME I. BRODY, M.D. 413

Progress of Medical Science

Oto-Rhino-Laryngology—Labyrinthine (Vestibular) Function Tests. I. Techniques. By A. HARRY NEFFSON, M.D. 421

Dermatology and Syphilology—Pigmented Nevi and Malignant Melanoma of the Skin. A Survey of Some of the Recent Literature. By HERMAN BEERMAN, M.D., R. A. G. LANE, M.D., and BERTRAM SHAFFER, M.D. 444

Physiology—Proceedings of the Physiological Society of Philadelphia, December 21, 1954 466

Book Reviews and Notices 469

Complete contents on adv. page 8

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*Blood Pressure, Report of Joint Committee on Mortality of The Association of Life Insurance Medical Directors and The Actuarial Society of America, New York, 1925, pp. 10, 52.

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CONTENTS

ORIGINAL ARTICLES

Effects of Chlorpromazine in Psychiatric Disorders 355
By IRVIN M. COHEN, M.D., Galveston, Texas.

Chlorpromazine in the Treatment of Acute Alcoholism 363
By EARL H. MITCHELL, M.D., Washington, D. C.

Multivalvular Involvement in Rheumatic Heart Disease with Particular Reference to Cardiac Surgery 368
By JACQUES B. WALLACH, M.D., LESLIE LUKASH, M.D., and ALFRED A. ANGRIST, M.D., Jamaica, New York and Bronx, New York.

The Fibrinogen Polymerization Test in Active Rheumatic Disease . . . 371
By SAMUEL LOSNER, M.D., and BRUNO W. VOLK, M.D., Brooklyn, New York.

The Value of Parenteral Reserpine in Acute Hypertension 379
By FRANK A. FINNERTY, JR., M.D., and JAMES G. SITES, M.D., Washington, D. C.

(Contents continued on page 10)

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CONTENTS (*Continued*)

The Possible Therapeutic Value of Cholecystectomy in Adams-Stokes Disease 386
By GEORGE A. MCLEMORE, JR., M.D., and SAMUEL A. LEVINE, M.D., Boston, Massachusetts.

The Effects of an Adrenergic Blocking Agent, Regitine, Upon the Glucose Tolerance Curve in Peptic Ulcer Patients 392
By MARGARET HAY EDWARDS, M.D., and THOMAS K. RATHMELL, M.D., Trenton, New Jersey.

Esterase and Lipase Activity of Leukocytes and Erythrocytes in Health and Disease 397
By E. BARTON HARDIN, M.D., WILLIAM N. VALENTINE, M.D., JAMES H. FOLLETTE, M.D., and JOHN S. LAWRENCE, M.D., Los Angeles, California.

Acquired Agammaglobulinemia with Hypersplenism. A Case Report . . 406
By ROBERT J. ROHN, M.D., ROY H. BEHNKE, M.D., and WILLIAM H. BOND, M.D., Indianapolis, Indiana.

Clinical Pathological Conference 413
By HERMAN W. OSTRUM, M.D., PAUL GYORGY, M.D., and JEROME I. BRODY, M.D., Philadelphia, Pennsylvania.

(Contents continued on page 12)

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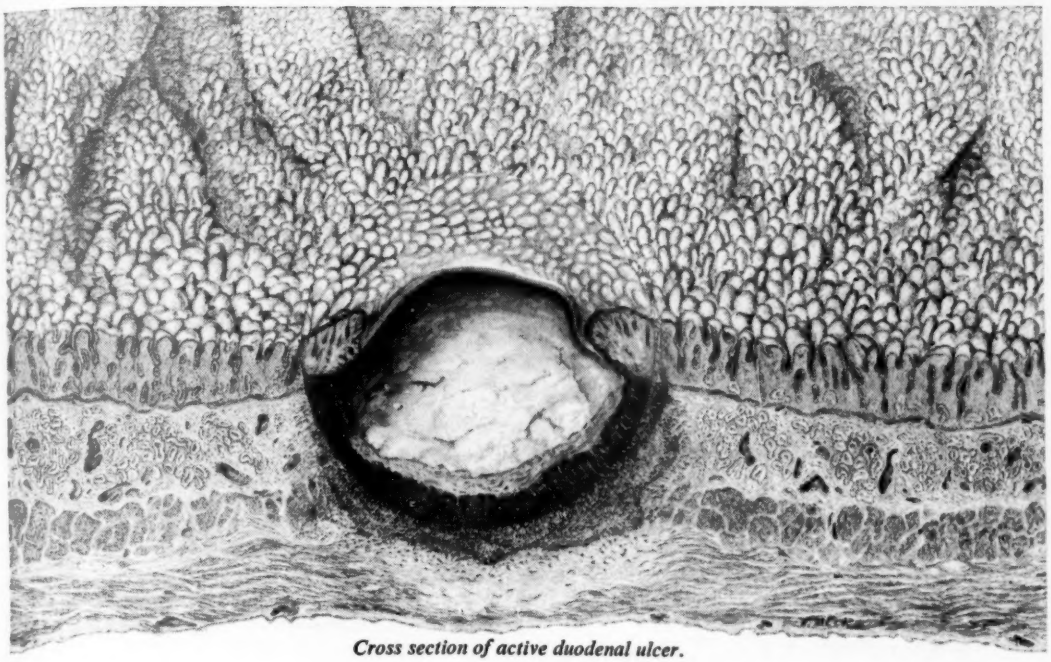

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

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(Contents continued on page 14)

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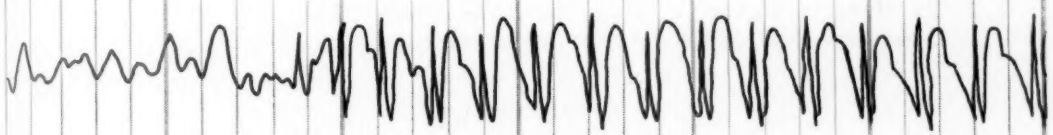

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CONTENTS (*Continued*)

OTO-RHINO-LARYNGOLOGY

Labyrinthine (Vestibular) Function Tests. I. Techniques 421
By A. HARRY NEFFSON, M.D., Tucson, Arizona.

DERMATOLOGY AND SYPHILOLOGY

Pigmented Nevi and Malignant Melanoma of the Skin. A Survey of Some of the Recent Literature 444
BY HERMAN BEERMAN, M.D., R. A. G. LANE, M.D., and BERTRAM SHAFFER, M.D., Philadelphia, Pennsylvania.

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Proceedings of the Physiological Society of Philadelphia, December 21, 1954 466

Book Reviews and Notices 469

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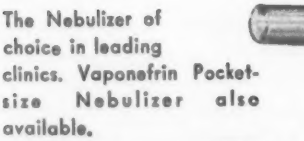

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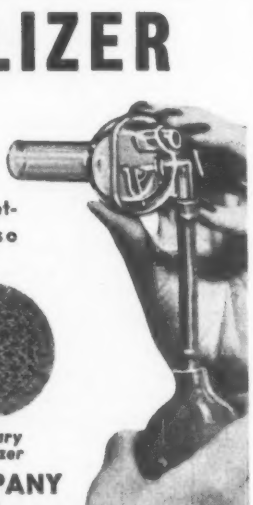

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APRIL, 1955

ORIGINAL ARTICLES

EFFECTS OF CHLORPROMAZINE IN PSYCHIATRIC DISORDERS

REPORT OF CLINICAL OBSERVATIONS AND IMPRESSIONS IN 1000 CASES*

By Irvin M. Cohen, M.D.
ASSISTANT PROFESSOR OF NEUROLOGY AND PSYCHIATRY

(From the Department of Neurology and Psychiatry, University of Texas Medical Branch, Galveston, Texas)

Since becoming commercially available in the United States in May, 1954, chlorpromazine (Thorazine, S.K.F.) has rapidly achieved widespread usage to a degree seldom accorded a new drug. A rapidly accumulating literature, particularly from Europe where the drug was first introduced, contains reports of its employment in almost every field of clinical medicine. Nevertheless, its ultimate place in therapeutics remains to be determined.

Investigation of the possibilities of chlorpromazine in the treatment of psychiatric illness was begun at the University of Texas Medical Branch in March, 1954. Appraisal of any substance in regard to effects on psychic functions always presents certain difficulties because of the fluidity of diagnostic criteria in psychiatry and the impossibility of accurately quantifying results. In the case of chlorpromazine these factors have been complicated by what appears to be an unusually broad spectrum of application, wide variability of response, and often incomprehensible effects. The range of results has in fact been so wide as to indicate that exceptionally prolonged study will be required before definitive conclusions concerning its efficacy can be reached. This paper is therefore intended as a report of relatively early clinical observations and impressions of the utility of chlorpromazine in the management and treatment of psychiatric disorders, rather than as a detailed statistical analysis of data.

Pharmacology. Chlorpromazine was first synthesized in France in 1950, during the course of a laboratory investigation of the antihistaminic drugs. It had been found that certain of the phenothiazine derivatives, notably Phenergan, exhibited not only antihistminic action but hypnotic and analgesic effects as well and were thus capable of potentiating anesthetics. However, their capacities to do so

*This study was done with the collaboration of Dr. Titus H. Harris (Chairman), Dr. Hamilton Ford (Professor) and other members of this Department.

Portions of the chlorpromazine (Thorazine) used in this study were supplied by Smith, Kline & French Laboratories, Philadelphia.

were too weak to be clinically significant, and a search was made for a compound with greater activity in these directions. Chlorpromazine, a chlorinated phenothiazine derivative like Phenergan but with little antihistaminic action of its own, was found to possess not only the desired properties but also powerful muscular relaxing, hypothermic, and antiemetic activities. Though originally introduced as an adjunct in anesthesia and surgery, its usefulness in psychiatry was quickly recognized. Early clinical trials in the United States began in the latter part of 1952, and on May 15, 1954, it was made available commercially.

The sites of its physiological action are still ill-defined. Clinically the manifestations are referable to all three divisions of the nervous system: central, autonomic, and peripheral, but there is strongly suggestive evidence that the primary effect may be in the diencephalic area. Though the drug produces sleep, it does not seem to do so through depression of the cortex as in barbiturate narcosis. This feature is clinically significant, in that the patient in chlorpromazine sleep can easily be awakened and responds in relevant and coherent fashion, in contrast to the hypnosis of barbiturates where the patient is cloudy, befogged, and even disoriented as a result of cortical depression. In relation to the autonomic nervous system it acts as a ganglioplegic and adrenolytic agent, so that both sympatholytic and parasympatholytic effects, principally the latter, are noted. Peripherally it produces a profound muscular relaxation.

Its mode of action is a subject of great speculation. From a strictly psychological perspective one may reason that improvement in the psychological state takes place through some unique method of attack on anxiety as the common denominator of psychiatric illness. It has also been suggested that the drug interrupts conditioned psychological responses[5] in the same manner by which it interrupts conditioned reflex responses[1]. A third explanation may be that psychological illness is in reality based on some yet unknown physiogenic brain dysfunction salutarily affected by the drug.

Material. Experiences reported in this study cover a period of 9 months, and have been drawn from a series of approximately 1000 cases. Case material included patients hospitalized on the Psychiatric Services of the John Sealy Hospital and at St. Mary's Infirmary, and outpatients of the Neurology and Psychiatry Clinic of the John Sealy Hospital. All were being treated for psychiatric illnesses of various types. Although other methods of therapy were often used in conjunction with chlorpromazine, the observations described are those which are regarded as peculiar to the drug.

Clinical Applications. 1. NAUSEA AND VOMITING. With rare exceptions, psychogenic nausea and vomiting have responded favorably to the administration of chlorpromazine. It was also effective in cases of nausea and vomiting due to physical disease coexisting with psychiatric symptomatology. Specifically, these have included cases of carcinomatosis, pregnancy, acute alcoholic gastritis, and dumping syndrome. In one case of dumping syndrome following sub-total gastric resection, emptying time on roentgenographic examination was found to have returned to within normal limits during treatment with chlorpromazine. It was also found to be useful in relieving nausea and vomiting occasionally accompanying insulin shock therapy and electro-convulsive therapy.

The doses required were consistently small, usually but 25 to 50 mg., three to four times per day, administered orally or intramuscularly as the case required.

2. FUNCTIONAL PSYCHIATRIC DISORDERS.

The results of chlorpromazine in the treatment of the so-called functional psychiatric disorders have been highly variable and very individualized, there being little uniformity in degree or quality of therapeutic response. Patients with identical diagnostic labels and nearly identical symptom pictures have not necessarily derived identical results. Consequently, we have as yet been unable to establish any specific nosological indications for the use of this drug. Improvement apparently did not depend on diagnosis, but rather on the presence or absence of certain clinical features in the illness. Thus we have found the best results occurring in those cases in which the most prominent manifestations have been (1) agitation, (2) anxiety, or (3) aggression. It is probably safe to say at the present level of our knowledge of the mode of action of this drug that it is principally of use in symptomatic control. However, in some cases in which dramatic results have occurred, one almost suspects that there may be some actual curative effect, the nature of which is still unknown.

Agitation. It is in the reduction and control of agitation that chlorpromazine has proved most useful. The term agitation is used here in the connotation of an increase in motor activity, ranging from moderate motor restlessness to violent excitement. Hyperactivity of this sort is most commonly seen in psychotic patients and consequently usually presents some problem in management. Prevention of exhaustion and maintenance of nutrition under such circumstances are often difficult, so that intravenous sedation and tube feedings may be required, procedures which themselves are not without hazard. In such situations chlorpromazine has proved to be of singular value. Its capacity to convert highly disturbed behavior into docile tractibility has remained an impressive phenomenon. Typically, approximately 30 to 40 minutes after intramuscular injection of 50 to 100 mg. of chlorpromazine, the disturbed patient is noted to lie down and fall asleep. The facies is sallow and pale, respiration is slow and deep, blood pressure is reduced, and pulse rate is increased. Despite the depth of sleep, the patient may be awakened easily; if the patient cannot be awakened another factor other than chlorpromazine is present. The patient responds to questions in brief but adequate manner and passively follows commands, quickly falling asleep when left alone. Control of behavior has been maintained with repeated injections. However, in the case of highly disturbed patients, out of caution we have generally not depended on chlorpromazine alone, but have subsequently instituted electroshock therapy because of the proven efficacy of this method. Agitation has been relieved in less disturbed patients without the necessity of combining it with electroshock treatment. This approach has been most frequently indicated in those patients having severe myocardial damage or similar contraindications to electroshock treatment. The diagnostic categories showing disturbed behavior in which chlorpromazine has been applied with success include paranoid and catatonic schizophrenia, agitated depression, and the manic phase of the manic-depressive psychosis.

Anxiety. Patients who complained of "nervousness," tension, vague feelings of unrest, and similar indicators of the presence of freely floating anxiety generally responded well to chlorpromazine. In contrast, patients who displayed little anxiety, or who were withdrawn, derived little benefit. Results were also poor if the anxiety was fixated to an organ or situation, or if there

was secondary gain from symptoms in the form of familial sympathy or overindulgence. Thus it has been of value in the anxiety states, panic reactions, acute obsessional neuroses, and some cases of schizophrenia. Results were ordinarily disappointing in hysteria, the usual depressions, hypochondriasis, obsessive-compulsive and phobic neuroses, and chronic (simple) schizophrenia. In successful cases a type of relaxation and calmness was induced which apparently differs from that produced by narcotics and barbiturates. Whereas in the latter there is temporary replacement or alteration of reality with some degree of clouding of the sensorium, chlorpromazine reduced the level of emotional tension with little loss of efficiency. In addition, by virtue of its complex pharmacodynamic effects, there was diminution of many distressing autonomic symptoms. Purely as a sedative it functioned efficiently in 50% to 60% of cases in which anxiety was marked. Complete remission of symptoms has occurred in about 10% to 15% of neurotic patients treated with the drug alone.

Aggression. In a significant number of cases, chlorpromazine has been noted to exert a curious specificity against thoughts and actions of an aggressive quality. It should be noted that ideation and behavior of this character are nonspecific, and may appear in any category of psychiatric illness. The mode of expression, however, assumes many forms. Thus, hostility may be manifested as excessive irritability in any hysteric, or in persecutory delusions of the paranoid schizophrenic. It may more directly reflect the particular underlying conflict, as in the example of the inhibited man plagued by feelings of inadequacy who becomes an expansive, bellicose manic. This aspect of the drug's action has been most evident in the resolution of hypomanic and manic phases of the manic-depressive psychoses, and particularly in some cases of paranoid schizophrenia. In the latter we have seen remarkable instances of complete remission of symptoms, disappearance of paranoid delusions, and production of insight into the nature of the illness. The following examples may be cited. One patient, who in the past had remitted on a program of combined electroshock and deep insulin therapy but had relapsed, remitted once again on chlorpromazine alone. Another patient, who had not responded to electroshock therapy, deep insulin coma therapy, or lobotomy, completely remitted on the drug alone. Large doses were a consistent requirement in all such cases. The action of chlorpromazine in the management of states of anxiety and agitation can perhaps be easily understood on the basis of its sedative properties, but its ability to attack this class of symptoms is difficult to comprehend.

3. ORGANIC PSYCHIATRIC DISORDERS. Our experience in the use of this drug in organic psychiatric states has been limited to the treatment of post-alcoholic delirium tremens, agitated senile-arteriosclerotic psychoses, post-encephalitic psychoses, and post-traumatic personality disorders.

Its use in delirium tremens has been very encouraging, there being strong indication that the duration of delirium is materially reduced when the drug is used. In each case the drug was used in conjunction with the usual routine of fluid-glucose-electrolyte replacement, diet, therapeutic vitamin regimens, and anticonvulsant drugs. The necessity for administering barbiturates and paraldehyde has almost been eliminated, thus obviating the possibility of replacing alcoholism with habituation to these sedatives.

Very satisfactory results were ob-

tained in the management of senile and arteriosclerotic patients manifesting protracted agitation or periodic excitement. Sedation of the aged patient often poses a difficult problem. Barbiturates occasionally aggravate excitement, effects may be unsustained, or such large amounts are required that their use is accompanied by risk of respiratory depression. In the aged patient only small amounts of chlorpromazine have been required to produce a tranquilizing effect. Reduction in hyperactivity was unfortunately the only improvement obtained in these cases, the mental status remaining otherwise unchanged except where malnutrition as a result of refusal to eat was a factor.

One case of postencephalitic psychosis has been treated, the only benefit being in the sphere of control of behavior. In 3 cases where personality disorders followed head injury, irritability was moderately reduced.

Dosage. To date we have been unable to establish any standard dosage requirement for the treatment of any particular psychiatric illness. Therapeutically effective dosage has proved to be an individualized quantity, to be determined entirely on the basis of clinical response. Thus, the principle of increasing the dosage to the level of therapeutic effectiveness or appearance of toxic signs has been found to be the most reliable guide during administration. Dosage level and severity of illness apparently bear no interrelationship. A highly disturbed patient suffering from delirium tremens might require but 50 mg. four times a day, given intramuscularly, whereas an anxious neurotic might require 800 mg. per day for control of symptoms. Furthermore, following the establishment of a therapeutically effective dosage level, either tolerance or diminished requirement may develop, so that elevation or decrease of dosage may be required during the course of therapy.

In our series it was found that larger dosages were required than those described in previous reports. We believe that many failures with chlorpromazine can be attributed to the fact that insufficient dosage had been used. We have found clinically effective levels to lie more frequently in the range of 200 to 800 mg. daily than within the previously recommended range of 50 to 200 mg. daily. In general, the dosage required for improvement of neurotic disorders has been approximately 200 to 600 mg. daily, whereas psychotics have usually required at least 400 to 800 mg. daily. Improvement usually occurred within the first 2 to 3 weeks after treatment had begun; in some cases improvement was obtained later when the dose had been elevated to a higher and hence therapeutically effective level. To date the maximum dosage which we have administered has been 2250 mg. daily. Other investigators have reported giving as high as 3400 mg. daily without appearance of toxic signs[4].

Rapid effect can be obtained by intramuscular administration; however, repeated injections have been accompanied by the development of marked soreness and tenderness at the site of administration. Our custom in the treatment of highly disturbed patients or in patients in whom rapid effect was desirable has been to administer 50 mg. intramuscularly every 4 to 6 hours. If this dose was found to be inadequate for control of symptoms subsequent doses might be increased to 100 mg. each. If satisfactory response was obtained in 24 to 72 hours by this route, oral medication was partially or totally substituted. Oral dose was increased thereafter each day as indicated. In cases where extremely rapid control of symptoms was not necessary, as was true in most neurotics and psychotics,

the oral route was used exclusively. Hospitalized patients were begun on 50 mg. every 6 hours, the dose being increased each day or every other day. In non-hospitalized patients, in an effort to ascertain the intensity of side-effects which might develop, the initial dose has been 25 to 50 mg., one to four times per day, increasing in increments of equal quantity to the desired therapeutic level.

At times it has become necessary to administer barbiturates to patients receiving chlorpromazine. It has been found in such cases that barbiturates in the usually recommended oral doses can be given with safety, notwithstanding the reported potentiating action of chlorpromazine[6].

The question of how long treatment should be continued has remained unsettled. In general, psychotics and severe neurotics have been placed on maintenance doses, whereas treatment of most neurotics has generally been discontinued simultaneous with symptomatic relief.

Side-Effects. The side-effects of chlorpromazine are numerous and varied, and have appeared in one degree or another in almost every patient to whom the drug has been administered. Although temporarily distressing to the patient, they have not necessitated discontinuation of treatment unless extremely severe. Most appeared early and were independent of the dosage level. However, side-effects of a different character developed 2 or 3 weeks after treatment had begun in approximately 10% to 15% of the patients. In contrast to the early side-effects which were of temporary duration, the later side-effects tended to be persistent and could more nearly be correlated with the increasing dosage.

The most common subjective complaints noted during the early phases of treatment included dizziness related to postural changes, profound and often annoying weakness, lethargy, dryness of the mouth, and nasal congestion. Less common but not infrequent were a burning sensation in the esophagus, nausea and vomiting, and constipation. Objectively the most impressive finding was fall in blood pressure. This occurred most dramatically following parenteral administration. Usually within 30 to 40 minutes after injection readings would drop 30 to 50 mm. systolic and 20 to 30 mm. diastolic, associated with compensatory tachycardia. Despite this precipitous fall, there was no case of circulatory collapse in any of our patients. Hypotension also developed during oral administration, but was more commonly of an orthostatic type. Lowered blood pressure was quite temporary with rapid return to former levels as treatment progressed. Syncopal attacks were rare and occurred only in cerebral arteriosclerotic psychotics, who were naturally more sensitive to momentary cerebral vascular hypotension. Hypersomnolence occurred at all levels, but usually began when oral doses of greater than 200 mg. daily were given. Generally there was no interference with nocturnal sleep, even though diurnal sleep might have been as much as 10 hours. Although sedation of this type was useful in disturbed patients, it often distressed otherwise ambulatory patients. In the latter case small doses of sympathomimetic drugs were sufficient to counteract it. Other early findings included facial pallor, hypothermia or hyperthermia, and slowing of movement.

Late effects included excessive appetite, blurring of vision, intense pruritus, photosensitization, rest tremor, and increased sexual urge. Quite often a sudden spike of fever, not associated with evidence of infection or leukocytosis, took place. Swelling of the

breasts and secretion of a colostrum-like fluid from the nipples were occasionally noted in female patients.

Complications. Of greater concern were certain side-reactions which we arbitrarily classed as complications, mainly on the basis of their potentially serious quality. However, with the possible exception of a single case, recovery has been spontaneous and rapid. No deaths directly attributable to the drug occurred in this series.

The most frequent complication was dermatitis, which occurred in about 10% of cases. Though occasionally preceded by intense itching, unresponsive to antihistamines, it usually appeared suddenly about 2 to 3 weeks after treatment had been started and was unrelated to dosage level. Most commonly it was in the form of a maculopapular rash confined to the sides of the neck and upper chest. Spread to the trunk and extremities occurred in about one-third of these cases. Somewhat less frequently it occurred as an erythema multiforme, at times associated with either swelling of the face or generalized edema. Generalized urticaria was noted occasionally. With the exception of those cases in which there was an accompanying edema, the dermatitis usually cleared in about 3 to 4 days despite an often florid appearance. In no case was it necessary to resort to steroids. Chlorpromazine was discontinued only when the eruption was generalized or when there was intense subjective distress. In most of these cases it was subsequently reinstituted with no recurrence of the dermatitis in any case. One patient who had become photosensitive developed a maculopapular rash on exposure to sunlight, which subsided within 2 hours after return indoors.

Jaundice occurred in 6 patients (less than 1%) in this series. Results of laboratory studies in these instances consistently indicated an obstructive process within the biliary system, and no evidence of cellular damage. In the majority of cases icterus appeared approximately 3 weeks after chlorpromazine had been instituted and was not related to dose. Usually the patient complained of mild general malaise, persistent or intermittent nausea, occasional vomiting, and vague abdominal pain. The succeeding clinical course in each case was uneventful, disturbing symptoms disappearing within several days, icterus clearing within 2 to 3 weeks. Treatment was of a supportive nature, consisting mainly of withdrawal of the drug, intravenous glucose when indicated, therapeutic vitamin regimen, and high-carbohydrate, high-protein, low-fat diet. In one case the drug was reinstituted without recurrence of the jaundice. Cohen and Archer reported that prolonged administration of chlorpromazine was not accompanied by hepatotoxic effects, and have concluded that the appearance of jaundice is a random effect, in all probability based on an allergic reaction to the drug[3].

A most interesting and perhaps significant complication has been the occasional development of Parkinsonism with typical masking of the facies, stooped posture, loss of associated movements, rigidity, and tremor. Rigidity has been more prominent than tremor. These cases have appeared in any age group, usually when dosages exceeding 400 mg. daily were given. The syndrome has cleared in 5 to 14 days following withdrawal of the drug. However, in one patient the syndrome persisted until his death from uremia some 4 months later.

Other complications noted have been dependent edema, one instance of nonfatal anaphylactoid reaction, and 2 deaths due to pneumonia. The latter may be regarded as an indirect but

preventable complication; both were elderly patients who in all probability suffered pulmonary hypostasis as a consequence of chlorpromazine-induced hypersomnolence.

Fatal agranulocytosis has recently been reported by Boleman[2]. Rare instances of leukopenia and eosinophilia have been encountered in this series, but agranulocytosis has not occurred.

Summary. Variability in clinical response and wide range of effects have made evaluation of chlorpromazine as a therapeutic agent in psychiatry difficult. From a nosological standpoint, the spectrum of this drug has included psychiatric illnesses of all classifications. However, experience in 1000 cases of psychiatric disorders of both functional and organic etiology has indicated that it is most effective if there is evidence of (1) agitation, (2) anxiety, or (3) aggression, irrespective of the specific diagnostic entity in which the manifestation may appear. In approximately 60% of the cases in this series improvement was derived, which varied in degree from mere reduction in intensity of symptoms to apparently complete resolution of illness. Only with extended observation will it be possible to determine if the latter represents temporary remission or absolute recovery. The dosage that may be required is a highly variable quantity which must be individualized and determined strictly on the basis of clinical response. It is believed that many failures with chlorpromazine can be attributed to the fact that inadequate dosages are used. In this series effective dosage for neurotics has been in the range of 200 to 600 mg. daily, whereas psychotic patients have generally required 400 to 800 mg. daily. As much as 2250 mg. daily has been administered without toxic effects. Side-effects of one sort or another have occurred in almost every patient, but only rarely did treatment have to be discontinued because of them. Those which appeared very early were generally transient and unrelated to dosage level, while those appearing during the later phases of treatment when doses were higher tended to be persistent. Complications involving widely dissociated organ systems have been observed, but all have proved to be benign, despite often immediately alarming proportions. Fatal agranulocytosis has recently been reported but has not been observed in this series.

REFERENCES

1. **Archer, J. D.:** Fed. Proc., **13,** 332, 1954.
2. **Boleman, A. P.:** J. Am. Med. Assn., **157,** 364, 1955.
3. **Cohen, I. M.,** and **Archer, J. D.:** A Study of Liver Function and Hepatic Complications in Patients Receiving Chlorpromazine. Presented at the Second Joint Meeting of the Neuropsychiatric Society of Mexico and the Texas Neuropsychiatric Association, Galveston, October, 1954. To be published.
4. **Kinross-Wright, V.:** Complications of Chlorpromazine Treatment. To be published.
5. **Leake, C. D.:** Personal communication to the author.
6. **Leborit, H., Huguenard, P.,** and **Alluame, R.:** Presse méd., **60,** 206, 1952.

CHLORPROMAZINE IN THE TREATMENT OF ACUTE ALCOHOLISM

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This study has been made on 306 sanitarium patients representing 400 consecutive admissions for acute alcoholism. One half of this group received chlorpromazine as the primary therapeutic agent and one half received barbiturates and mephenesin for sedation. This report outlines the results of treatment and complications encountered in each of these groups.

Clinical Material. The chlorpromazine group represented 156 patients of whom 126 had one admission to the hospital and 30 patients who had multiple admissions during the period of study. The other group represented 150 patients with one admission and 30 having multiple admissions. Most patients in both groups were employed and were brought to the sanitarium by a member of their family, a friend, or a member of Alcoholics Anonymous. Admission to the sanitarium was voluntary in each case and each patient was at liberty to sign a release and leave the hospital at any time. The staff made every possible effort to persuade each patient to remain in the hospital for a minimum period of 5 days.

Figure 1 shows the age distribution of patients in both groups, indicating that the average patient was 40 to 50 years of age in both groups. Male patients outnumbered female patients by 3 to 1. Each group of 200 admissions represented all patients entering the hospital during a period of 3 months. There were 74 readmissions in the chlorpromazine group and 80 readmissions in the barbiturate group.

In both groups several resources were utilized to effect rehabilitation while detoxification was being accomplished. It was felt that during the withdrawal period many alcoholics are most receptive to suggestions regarding rehabilitation. The sanitarium has excellent cooperation from members of Alcoholics Anonymous, who frequently counsel patients who are interested in recovery from alcoholism. A.A. meetings were held in the hospital, and were designed to explain the A.A. program to those patients who were interested.

Upon discharge those patients who were found to have medical problems that required treatment beyond the period of hospitalization were referred to their own family physician. Other patients were referred to the District of Columbia Alcoholic Rehabilitation Clinic or to private psychiatrists. It is beyond the scope of this report to discuss the results of treatment after leaving the sanitarium, but the difficulty of effective rehabilitation during short-term therapy may be seen in Figures 2 and 3 showing the number of readmissions in each group.

Method of Treatment. In both groups treatment was directed toward correction of dehydration and electrolyte balance, avitaminosis, and malnutrition. No alcohol was given to any patient. Both groups received 1,000 to 1,500 cc. of 5% glucose in physiological saline solution with vitamin B complex and vitamin C added to the solution. All patients received an injection of vitamin B complex with vitamin C intramuscularly each day during their hospital stay. Chloral hydrate, 1.0 to 1.5 gm., was given at bedtime to all patients in the barbiturate group and to those patients in the chlorpromazine group who were not asleep at bedtime. In both groups the amount of chlorpromazine and barbital was progressively diminished so that upon leaving the hospital patients were receiving only vitamins and minimal or no sedation.

Upon admission the chlorpromazine group received 50 mg. of chlorpromazine* intra-

*The chlorpromazine was furnished by Smith, Kline & French Laboratories, Philadelphia.

muscularly or 50 mg. added to the intravenous solution. After this dose, if the patient could retain oral medication, 50 to 100 mg. was given each 4 hours. Patients who weighed less than 125 pounds received 50 mg. and patients who weighed more than 125 pounds, 100 mg. of chlorpromazine.

The barbital group received 250 mg. of secobarbital in the intravenous solution or in the intravenous tubing. This group also received butobarbital, 60 mg., and mephenesin, 1.5 gm., every 3 hours until bedtime.

Results. The outstanding difference in the two groups appeared to be the nature of the sedation afforded by chlorpromazine as compared with butobarbital or secobarbital. Patients who received chlorpromazine soon became quiet and dropped into light sleep, yet could be easily awakened to receive medication or nourishment. They were more amenable to sugges-

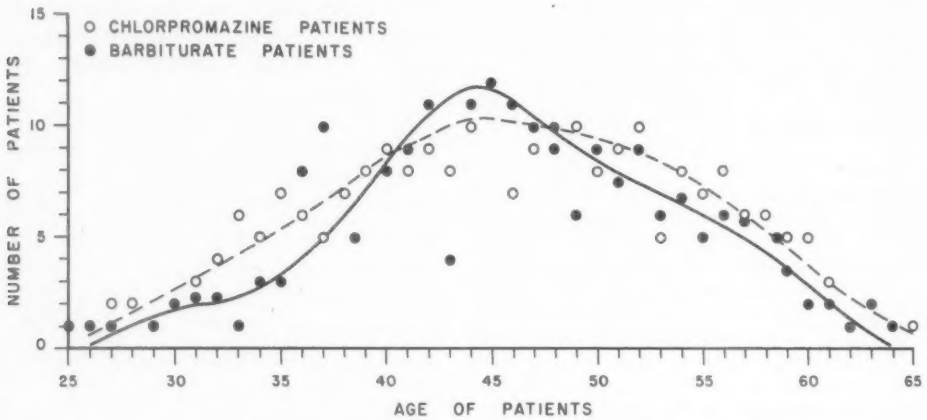

Fig. 1.—Scatter diagram showing age distribution of (°) patients receiving chlorpromazine and (●) patients receiving barbiturates.

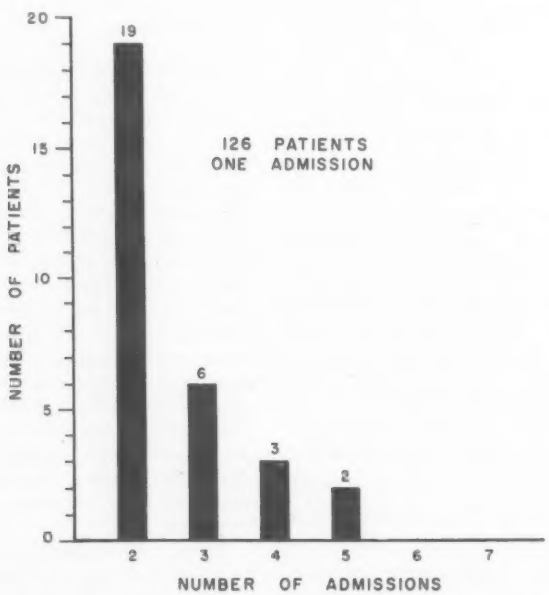

Fig. 2.—Number of patients receiving chlorpromazine and number of times readmitted.

tions from the nursing and medical staff. Sedation afforded by chlorpromazine was unusual in that the patient appeared to be aware of his environment but too relaxed and lethargic to react to it.

It was noted that chain cigarette smokers often would not light a cigarette for several hours, even though matches and cigarettes were lying on their bedside table. The nurses reported fewer falls from bed in the chlorpromazine group. A frequent difficulty with secobarbital sedation was the accompanying disturbance in equilibrium which caused frequent falls from bed or to the floor. No patients receiving chlorpromazine fell from bed while in the admission room.

Nausea and vomiting stopped 45 to 60 minutes after injection of chlorpromazine.

Epigastric pain in all cases of acute gastritis was absent after the first 24 hours. Secobarbital and butobarbital also afforded considerable relief from nausea and vomiting, but not to the degree afforded by chlorpromazine. The patients in the latter group were able to retain solid food 18 to 24 hours earlier than the barbital treated group.

Eighty-five per cent of the patients in the series receiving chlorpromazine were found to have marked drowsiness. This drowsiness was profound for 24 to 36 hours, then gradually was overcome, even though the chlorpromazine was maintained at the same level. This would suggest that a compensatory mechanism increases the tolerance to chlorpromazine after 24 to 36 hours.

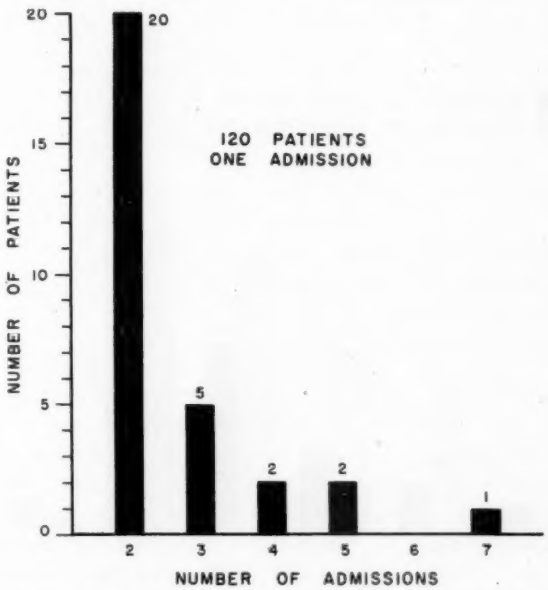

Fig. 3.—Number of patients receiving barbiturates and number of times readmitted.

Although 27 individuals in the chlorpromazine group exhibited clinical evidence of hepatomegaly and Laennec's cirrhosis, no jaundice was noted. It appears, that, even in the presence of fatty infiltration and parenchymal liver damage, chlorpromazine may be used for short periods with safety.

Figure 4 shows the number of days spent by each patient in the hospital.

It will be noted that in the chlorpromazine group the period of hospitalization was shortened an average of 24 hours, and this finding was substantiated by the clinical improvement noted. This appeared to be due to the ability of patients receiving chlorpromazine to retain fluids and nourishment sooner than the barbital treated group.

Since the readmissions in both groups were approximately the same, we believe that even though the hospital stay was shortened by 24 hours there was no appreciable difference in the readmission rate for the two groups. The period of hospitalization usually can be shortened by approximately 24 hours without adversely effecting the patient's chance of remaining sober after leaving the hospital.

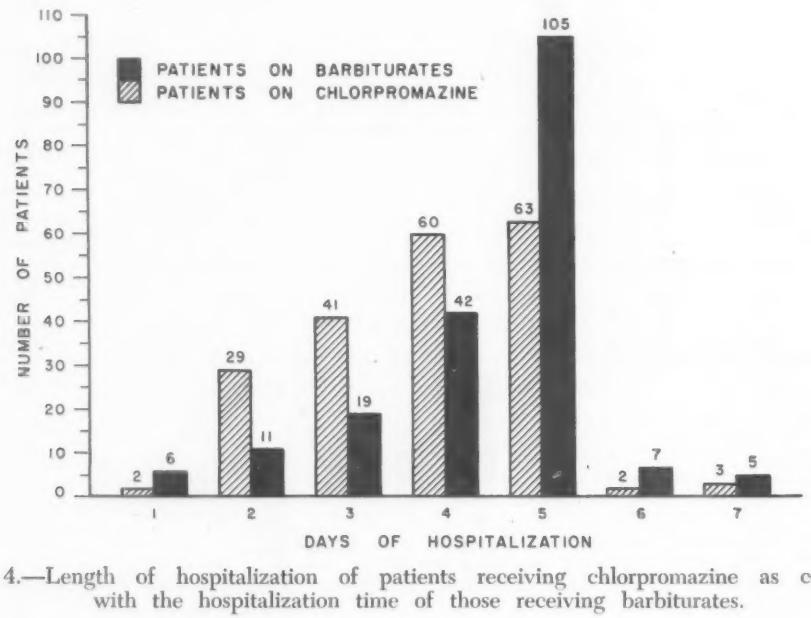

Fig. 4.—Length of hospitalization of patients receiving chlorpromazine as compared with the hospitalization time of those receiving barbiturates.

Complications. In 43 patients there was mild transitory postural hypotension. Seven additional patients had one or more severe hypotensive attacks. In each case the patient was either walking or sitting when he suddenly lost consciousness and fell. Consciousness returned in all cases within 30 seconds to 2 minutes. In all severe hypotensive attacks the patient was receiving 100 mg. of chlorpromazine every four hours. Upon reduction to 25 to 50 mg., no further difficulty was encountered. Palpitation and tachycardia were noted in 22 patients receiving chlorpromazine. The heart rate varied from 110 to 126, and in each of these patients produced noticeable symptoms, but the heart rate returned to normal when chlorpromazine was discontinued.

Three patients in the chlorpromazine group had one or more convulsive seizures and developed delirium tremens. In all 3 patients this complication developed between the third and fifth day of hospitalization, and all three cleared within 72 hours. No delirium tremens were seen in the barbital group. This suggests that secobarbital

and butobarbital have a prophylactic effect in the prevention of delirium tremens. Since chlorpromazine does not offer this protection, those patients who have had delirium tremens or alcoholic convulsions possibly should receive a small dose of barbiturates or other anticonvulsive drugs.

There was one death in the chlorpromazine group, under the following circumstances:

Case Report. A. R., a man aged 39, was admitted to hospital on April 17, 1954, and given chlorpromazine 50 mg. by mouth every four hours. On the evening of April 18, he had a sudden attack of syncope, quickly regained consciousness, but was confused 45 to 60 minutes afterwards. He apparently recovered, and continued to receive chlorpromazine.

A similar attack occurred on the morning of April 19, with return of disorientation and confusion. He died suddenly in the afternoon of April 19, two days after admission. Necropsy revealed congestive heart failure and advanced liver cirrhosis.

This is the only death in a series of 400 cases. It is suggested that extreme caution be exercised in treating severely debilitated, poor-risk patients with chlorpromazine until the therapeutic response to larger doses of the drug is more completely understood.

Summary and Conclusions. 1. In the treatment of 400 cases of acute alcoholism equally divided into chlorpromazine-treated and barbiturate-treated groups, the following regimens were carried out: Upon admission, the patients in the chlorpromazine group were given 50 mg. intramuscularly or by vein; after this they were given 50 to 100 mg. orally every four hours. The patients in the barbital group initially received 250 mg. of secobarbital intravenously, and 60 mg. butobarbital and 100 mg. of mephenesin every three hours until bedtime.

2. In those receiving chlorpromazine, a mild postural hypotension was noted in 43 instances (21%), and severe hypotension with syncope in 7 additional patients (3.5%). Severe hypotension was successfully controlled, by lowering the chlorpromazine dosage, in all but one case where the hypotension developed in a poor-risk cardiac patient with a cirrhotic liver who died two days after admission. Tachycardia was noted in 22 cases (11%). The heart rate returned to normal when chlorpromazine was discontinued.

3. Chlorpromazine appears to be a useful therapeutic adjunct in the detoxification of the acute alcoholic, having provided effective sedation in 85% of the 200 cases studied. In the chlorpromazine-treated group the nursing was simplified: the patients were more amenable to suggestions from the nursing and medical staff, there were fewer falls from bed, the patients could retain food earlier, and finally, as compared with the barbital group, they were in condition to be discharged from the hospital on an average 24 hours earlier.

MULTIVALVULAR INVOLVEMENT IN RHEUMATIC HEART DISEASE WITH PARTICULAR REFERENCE TO CARDIAC SURGERY

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As a result of the favorable experience with mitral commissurotomy surgeons have been encouraged to broaden the scope of operative procedures by enlarging the criteria for selection of patients having isolated valve defects, and by attempting simultaneous or consecutive correction of multivalvular lesions[2]. It would be of interest, therefore, to estimate the additional increment of patients who could benefit from multivalvular correction and to forecast any potential increase in risk to these patients from certain rheumatic cardiac complications (for example, embolism) to which they would be subject.

Material and Methods. As part of a larger study, a series of 8,676 consecutive necropsies performed at the Queens General Hospital from 1936 to 1950, inclusive, was reviewed[3]. Five hundred and nine (5.9%) of these were classified as rheumatic heart disease by fulfilling the following criteria: (1) fusion and retraction of the mitral or tricuspid valves; (2) fusion and shortening of the chordae tendinae; (3) noncalcific fusion of the aortic valve; (4) any fusion, including calcific changes, of the aortic valve when it was associated with definite rheumatic mitral valve involvement; (5) active rheumatic heart disease with Aschoff bodies or characteristic verrucae; (6) bacterial endocarditis of the mitral or aortic valves with some evident previous distortion, but the exact estimation of the severity of rheumatic damage being difficult. Cases showing the following changes were excluded from the rheumatic category: (1) slight mitral changes (for example, tongue-like extensions of the valve cusps), or distortion which did not fulfill the criteria stated above (points 1 and 2); (2) slight aortic stenosis with or without slight mitral involvement; (3) calcific aortic stenosis with or without slight mitral changes; (4) calcification of the valve rings alone. Thus, 103 cases of calcific aortic stenosis and 72 cases of doubtful origin were excluded from this study.

The severity of the rheumatic valvular stenosis was graded from 1 to 4 plus, with 1 plus being the least severe involvement, yet sufficient to meet the criteria above, and 4 plus being the most severe involvement and represented valves described as "fish-mouth," "button-hole," "slit-like," "markedly stenotic," "could not admit one finger"; 2 and 3 plus represented the intermediate degrees of severity.

In the present study, 82 cases with bacterial endocarditis were excluded. In addition, patients in the first 2 decades of life were not included because they usually showed evidence of rheumatic activity, and because patients in this age group are usually not accepted for cardiac surgery of this type. This paper is based on the 292 residual cases with severe (3 to 4 plus) rheumatic mitral or aortic stenosis, or both. Of these, the mitral valve alone was severely involved in 168 patients (58%),

the aortic valve alone in 33 instances (11%); both valves were severely affected in 91 hearts (31%).

Comment. The figures in the present study indicate that the number of patients eligible for cardiac surgery can be considerably increased (31%) by the surgical attack on multivalvular lesions. Since the present cases were chosen only on the basis of severe mitral and aortic involvement without regard to the clinical status of the patient or consideration of many other criteria used in the selection of patients for correction of valvular lesions, it is apparent that this represents a maximum estimate. This estimate can only be approached by the most careful clinical evaluation of these cases and by a realization of, and allowance for, the limitations in the diagnosis of these valvular lesions by clinical, laboratory and radiological techniques.

In a previous analysis[3a] it was demonstrated that in all cases of severe mitral stenosis (that is, with or without other valve involvement) antemortem thrombi occurred in the left auricle or the left appendage, or both, in 35.8%. In contrast, these thrombi were found only half as frequently (18.6%) in cases of severe mitral stenosis without severe aortic valve involvement. Thus the surgeon may expect to encounter these thrombi twice as often in candidates for correction of combined mitral and aortic stenosis. This study pointed out that the surgical mortality figures are much less than this incidence of mural thrombi and therefore embolization does not occur, or, when it does, usually involves tissues in a clinically silent fashion. The current use of compression of the carotid arteries during intracardiac manipulation[1] may further increase this discrepancy by diminishing the frequency of cerebral emboli.

It is worth noting, however, that thrombi in the chambers of the heart are not the only source of emboli. A previous study[3c] indicated that a large proportion of cases of rheumatic heart disease with infarcts have no associated mural thrombi and that nonbacterial thrombotic vegetations may be the significant source of embolism in these instances. A dislodged nonbacterial thrombotic vegetation may often be the actual source of the infarct even when mural thrombi are present in the chambers of the heart. Since vegetations of nonbacterial thrombotic endocarditis will not usually be seen or palpated, and therefore, not suspected by the surgeon, he should not be lulled into a false sense of security by not finding thrombi in the chambers of the left side of the heart. Since two valves will be manipulated during multivalvular procedures, the opportunity to dislodge emboli from these valves is approximately doubled and the surgeon should take such precautions as carotid compression during the manipulation of each valve. These precautions may prevent a possible clinical increase in the expected frequency of cerebral emboli. Such measures may well apply to the intracardiac approach for the correction of congenital heart diseases which are also a frequent basis for the development of nonbacterial thrombotic endocarditis.

Summary and Conclusions. In 292 necropsied cases of severe rheumatic heart disease, the incidence of mitral stenosis alone was 58%, aortic stenosis alone, 11%, combined severe mitral and aortic stenosis, 31%. Thus, on the basis of this series, 31% represents the additional maximal increment of patients which might benefit from the surgical correction of these multivalvular lesions.

The possible role of embolic nonbacterial thrombotic vegetations dislodged from the valve cusps is dis-

cussed. This potential increase in the frequency of emboli during these more extensive operative manipulations is stressed.

REFERENCES

1. **Bailey, C. P., Olsen, A. K., Keown, K. K., Nichols, H. T.,** and **Jamison, W. L.:** J. Am. Med. Assn., **149,** 1085, 1952.
2. **Bolton, H. E., Bailey, C. P., Jamison, W. L.,** and **Rao, K. V. S.:** J. Internat. Coll. Surgeons, **20,** 1, 1953.
3a. **Wallach, J. B., Lukash, L.,** and **Angrist, A. A.:** Am. Heart J., **45,** 252, 1953.
3b. Iidem: Am. J. Med., **15,** 77, 1953.
3c. Iidem: Am. J. Clin. Path., **24,** 172, 1954.
3d. Iidem: Am. J. Med., **16,** 543, 1948.
3e. **Wallach, J. B., Glass, M., Lukash, L.,** and **Angrist, A. A.:** Circulation, **9,** 908, 1954.
3f. Iidem: Ibid., **10,** 524, 1954.

THE FIBRINOGEN POLYMERIZATION TEST IN ACTIVE RHEUMATIC DISEASE

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It has been noted by us that considerable amounts of fibrinogen are preserved in serum after gross coagulation of a blood specimen has taken place, provided a therapeutic dose of heparin has been administered previously or after minute amounts have been added *in vitro* to a blood sample[14]. In view of the obvious presence of active thrombin, as generated by the process of coagulation, it has become evident that the antithrombic action of heparin is inadequate to account for incomplete coagulation and preservation of fibrinogen. It has, therefore, been concluded that heparin interferes with polymerization of fibrinogen in accordance with the theory of the transition of fibrinogen to fibrin as a two-step reaction[9]. Whereas heparin normally delays fibrinogen polymerization, as reflected in partial coagulation after a given time interval, the finding of complete clotting, that is total fibrinogen consumption under the same conditions, consequently indicates accelerated polymerization.

In the present study the mechanism of fibrinogen preservation in serum after heparin has been adopted as an indicator of either normal or accelerated fibrinogen polymerization. A procedure based upon this phenomenon has been elaborated and carried out in a variety of clinical conditions. It has revealed a marked acceleration of fibrinogen polymerization in both active rheumatoid arthritis as well as rheumatic fever. In contrast to the so-called "acute phase reactants"[1,6,7], it was found to be independent of the intensity of the inflammatory process or the therapeutic administration of cortisone. Moreover, the accelerated fibrinogen polymerization has been noted to persist long after other clinical and laboratory signs of rheumatic activity have subsided.

The purpose of the present report is to describe the technical details and to develop a rationale of the phenomenon of accelerated fibrinogen polymerization in active rheumatic disease.

Method. The procedure, termed by us "fibrinogen polymerization test" was carried out A) one hour after the intravenous injection of 50 mg. of heparin or B) without preliminary administration of heparin but after *in vitro* addition of 8 mcg. of heparin to 3 cc. of blood. This term was applied specifically to all procedures in which only these *critical* doses were utilized. In each instance 12 cc. of venous blood were withdrawn and distributed in 4 tubes, labeled 1 to 4 in aliquots of 3 cc. All blood specimens were placed in a waterbath and allowed to clot at 37° C. In order to stabilize the prothrombin content of the serum[20] 0.3 cc. of 0.1 molar sodium citrate was added to the clotted blood of tube 1 which was then centrifuged. Tubes 2, 3 and 4 were processed in identical fashion at hourly intervals. Citrate was added just before spinning down of the specimen. After centrifugation, the citrated serum was tested for the presence of fibrinogen by carrying out the photoelectric determination of prothrombin time[16] which allowed the

simultaneous estimation of the fibrinogen concentration according to the clot density method[17]. Coagulation of the incubated mixture of citrated serum and Difco-thromboplastin after addition of 0.02 molar calcium chloride was considered adequate evidence of the presence of fibrinogen in the particular serum. All specimens were run at hourly intervals for a period of 3 hours following gross coagulation in tubes 1 to 4.

MATERIAL. A) The *in vivo* fibrinogen polymerization test was carried out in 12 normal individuals one hour after the intravenous injection of 50 mg. of heparin. B) In another group, 12 normal individuals were subjected to the *in vitro* fibrinogen polymerization test by adding 8 mcg. of heparin to each aliquot of 3 cc. after withdrawing a total of 12 cc. of venous blood. C) The *in vivo* fibrinogen polymerization test was performed in 24 patients with a variety of clinical conditions, one hour after the intravenous injection of 50 mg. of heparin. D) The *in vitro* fibrinogen polymerization test as described above was carried out in 41 patients with various diseases. E) Tests which were identical in technique with the *in vitro* fibrinogen polymerization procedure, but utilizing 12 mcg. of heparin instead of 8 mcg. per 3 cc. of blood were done on 12 patients with active rheumatoid arthritis. F) Similarly, 12 patients, with active rheumatoid arthritis, received 75 mg. of heparin intravenously. One hour later 12 cc. of venous blood were withdrawn for a procedure identical with the *in vivo* fibrinogen polymerization test, as above.

INTERPRETATION. The fibrinogen polymerization test was considered *"negative"* whenever tube 3, which was centrifuged 2 hours after gross coagulation of the blood specimen, disclosed presence of unconsumed fibrinogen in the citrated serum. On the other hand, it was called *"positive"* whenever citrated serum obtained from tube 3 failed to coagulate upon addition of Difco-thromboplastin and calcium, thereby indicating complete consumption of fibrinogen. Examples of a positive and negative fibrinogen polymerization test are given in Tables 1 and 2, respectively.

Before carrying out the *in vitro* fibrinogen polymerization test, the clotting time of each heparin containing blood specimen was determined at 37° C. in 22 patients with active rheumatoid arthritis as well as in 12 normal individuals and 13 control patients.

TABLE 1.—EXAMPLE OF A *POSITIVE* FIBRINOGEN POLYMERIZATION TEST
(CITRATED SERUM OF TUBE 3 IS FREE OF FIBRINOGEN)

Twelve cubic centimeters in 4 aliquots of 3 cc. of blood, either withdrawn one hour after the intravenous injection of 50 mg. of heparin, or after the addition of 8 mcg. of heparin to each aliquot and distributed in:

	Tube 1		*Tube 2*		*Tube 3*		*Tube 4*	
	0.3 cc. of 0.1 Molar Sodium Citrate Added to Each Aliquot of 3 cc.							
Time Interval after Gross Coagulation	*Immediately after Clotting*		*1 Hour after Clotting*		*2 Hours after Clotting*		*3 Hours after Clotting*	
Hours	*P. T.**	*d***	*P. T.*	*d*	*P. T.*	*d*	*P. T.*	*d*
0	9.9	9	..	..	..	..	..	..
1	10.4	5	11.2	2.5	..	..	..	..
2	10.9	5	11.4	2	Fluid	..	..	..
3	11.7	4	13.2	1.5	Fluid	..	Fluid	..

* Prothrombin time (in sec.) of citrated serum determined according to the One-stage-Quick method.

** Fibrinogen concentration expressed in terms of clot density wherein F (plasma fibrinogen in mg. per 100 cc.) = 18d + 120.

Results. A) The intravenous injection of 50 mg. of heparin in 12 normal individuals revealed negative fibrinogen polymerization tests (Table 3).

B) Similarly, the *in vitro* fibrinogen polymerization test carried out in 12 normal individuals, was also negative (Table 4).

C) As seen from Table 3, 10 patients with active rheumatoid arthritis had positive *in vivo* fibrinogen polymerization tests. Another patient (H.M.), whose arthritic process was completely

arrested after ankylosis of both hips and knees, gave a negative *in vivo* fibrinogen polymerization test. She was a 48-year-old woman, whose illness began at the age of 20 with pain, swelling and limitation of motion in most small joints as well as both knees and hip joints. Signs of rheumatoid activity subsided about 10 years ago.

D) As seen from Table 4 the *in vitro* fibrinogen polymerization test gave results quite analogous to those obtained after the intravenous injection of 50 mg. of heparin. In this series 22 patients with active rheumatoid arthritis gave positive results while another inactive case was negative. Among the 5 patients with rheumatic fever in various

TABLE 2.—EXAMPLE OF A *NEGATIVE* FIBRINOGEN POLYMERIZATION TEST
(CITRATED SERUM OF TUBE 3 DISCLOSES THE PRESENCE OF FIBRINOGEN)

Twelve cubic centimeters in 4 aliquots of 3 cc. of blood, either withdrawn one hour after the intravenous injection of 50 mg. of heparin, or after the addition of 8 mcg. of heparin to each aliquot and distributed in:

	Tube 1		*Tube 2*		*Tube 3*		*Tube 4*	
	0.3 cc. of 0.1 Molar Sodium Citrate Added to Each Aliquot of 3 cc.							
Time Interval after Gross Coagulation Hours	*Immediately after Clotting*		*1 Hour after Clotting*		*2 Hours after Clotting*		*3 Hours after Clotting*	
	*P. T.**	*d***	*P. T.*	*d*	*P. T.*	*d*	*P. T.*	*d*
0	11.4	11	..	..	..	..	..	..
1	11.4	8	10.0	10	..	..	..	..
2	10.9	7	11.2	9	11.8	2.5	..	..
3	10.1	7	11.9	8	13.2	1.5	Fluid	..

* Prothrombin time (in sec.) of citrated serum determined according to the One-stage-Quick method.

** Fibrinogen concentration expressed in terms of clot density wherein F (plasma fibrinogen in mg. per 100 cc.) = 18d + 120.

TABLE 3.—*IN VIVO* FIBRINOGEN POLYMERIZATION TEST CARRIED OUT IN 36 INDIVIDUALS, GROUPED ACCORDING TO DIAGNOSIS AND RESULT

Diagnosis	*Number*	*Result*
Rheumatoid arthritis, active	10	+
Rheumatoid arthritis, inactive	1	—
Acute rheumatic fever, in various stages of activity	5	+
Decubitus ulcers	2	—
Generalized carcinomatosis	2	—
Rheumatic valvular heart disease with thromboembolic manifestations	1	—
Diabetes mellitus and intercapillary glomerulosclerosis	2	—
Disseminated lupus erythematosus with nephrotic syndrome	1	—
Normal individuals	12	—

Despite the ankylosis of both hips and knees, she was completely free from pain when the fibrinogen polymerization test was carried out. On clinical and laboratory grounds she was considered an arrested case. Eight control patients with a variety of clinical conditions had negative *in vivo* fibrinogen polymerization tests (Table 3).

stages of activity, serial determinations of the *in vitro* fibrinogen polymerization test at weekly intervals always produced positive results except in a few instances in one patient, G.G., a 16-year-old girl who was observed over a period of 4 months. While the clinical and laboratory signs of rheumatic activity subsided during a course of in-

tensive cortisone therapy the fibrinogen polymerization test remained uniformly positive almost to the end of steroid administration at which time it become negative. During the ensuing "rebound" it was found positive only to turn negative again and to remain so until her discharge (Fig. 1). Three of the 4 other patients with rheumatic fever received cortisone. The fibrinogen polymerization test remained unaffected by this therapy and was still positive at the time of their discharge.

Among 13 control patients with a

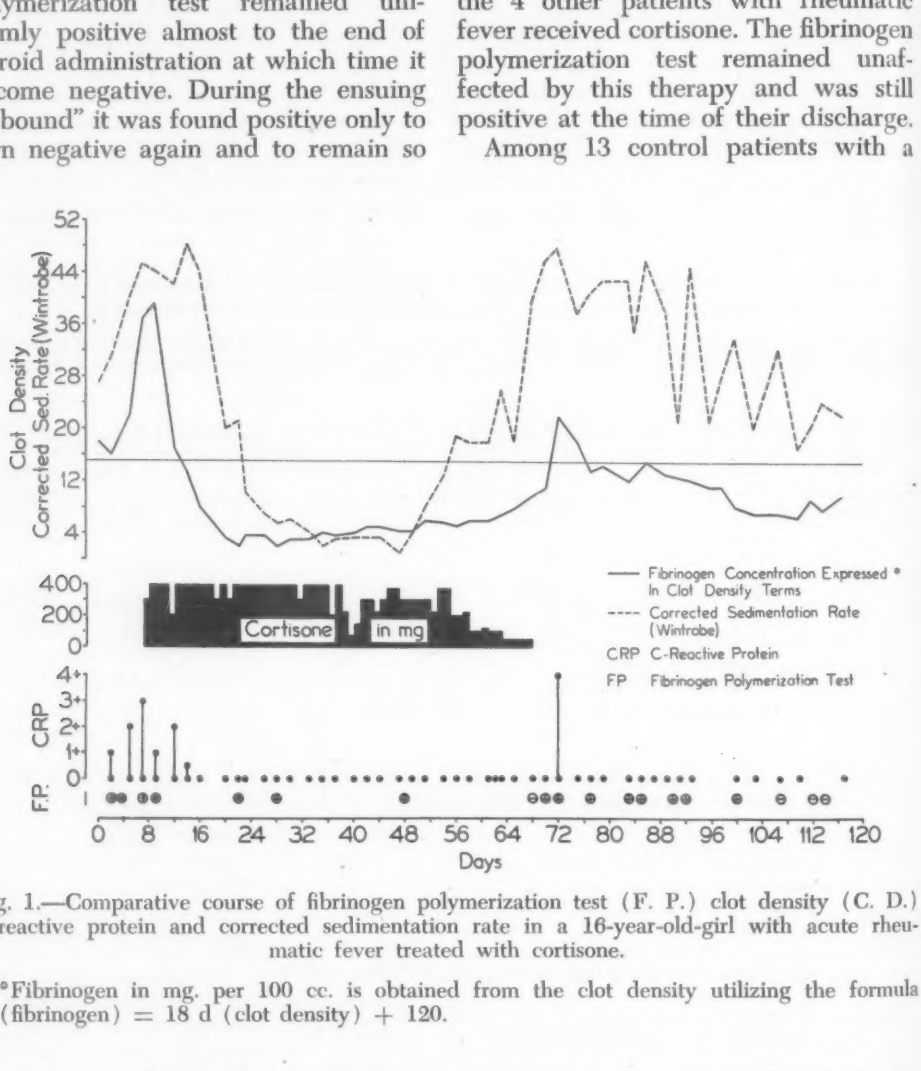

Fig. 1.—Comparative course of fibrinogen polymerization test (F. P.) clot density (C. D.) C-reactive protein and corrected sedimentation rate in a 16-year-old-girl with acute rheumatic fever treated with cortisone.

*Fibrinogen in mg. per 100 cc. is obtained from the clot density utilizing the formula F (fibrinogen) = 18 d (clot density) + 120.

TABLE 4.—*IN VITRO* FIBRINOGEN POLYMERIZATION TEST CARRIED OUT IN 53 INDIVIDUALS, GROUPED ACCORDING TO DIAGNOSIS AND RESULTS

Diagnosis	*Number*	*Result*
Rheumatoid arthritis, active	22	+
Rheumatoid arthritis, inactive	1	—
Acute rheumatic fever in various stages of activity	5	+
Diabetic gangrene	2	—
Laennec's cirrhosis	2	—
Coronary insufficiency	2	—
Decubitus ulcers in patients with paralysis agitans	3	—
Subacute glomerulonephritis	2	—
Secondary thrombocytopenic purpura due to chronic lymphatic leukemia	2	—
Normal individuals	12	—

variety of clinical conditions in whom the *in vitro* fibrinogen polymerization test was carried out, the results were always negative. These control patients were selected from disease groups ordinarily associated with both high fibrinogen concentrations, as diabetic gangrene or decubitus ulcers with very pronounced necrotizing processes, and also from other groups characterized by low fibrinogen levels, as in Laennec's cirrhosis. Most patients with rheumatoid arthritis also had high fibrinogen levels, thus indicating clinical activity. Two patients with secondary thrombocytopenic purpura due to chronic lymphatic leukemia revealed negative fibrinogen polymerization tests. The platelet counts in these patients were 40,000 and 60,000 per c.mm., respectively. No correlation between the platelet count and the fibrinogen polymerization test was, therefore, established.

E) The modified procedure, in which aliquots of 3 cc. of blood obtained from patients with active rheumatoid arthritis were added to 12 mcg. of heparin, revealed a pattern identical with the negative fibrinogen polymerization test as recorded in Table 2.

F) Similarly, the intravenous injection of 75 mg. of heparin also produced a pattern following that of the negative fibrinogen polymerization test as indicated in Table 1.

The mean clotting time of the heparin containing blood subjected to the fibrinogen polymerization test was 64 minutes in the group of specimens derived from patients with active rheumatoid arthritis. The same mean clotting time was obtained in the control group. The values ranged from 30 to 120 minutes in the arthritic individuals, while they varied from 31 to 120 minutes in the controls.

Discussion. Heparin is known to have multiple actions which interfere with the thrombinogenic cycle. While it is a powerful antithrombin[4] it also has been shown to have antiprothrombin[10,19] as well as antithromboplastic[2,13] properties. Very large doses of heparin have been claimed to cause a denaturation of fibrinogen[11,24]. In previous work[14] we have shown that considerable amounts of fibrinogen remain available in serum after gross coagulation of the blood specimen has taken place, provided that a therapeutic dose of heparin has been injected one hour before withdrawal of venous blood or when minute amounts of heparin have been added to a blood specimen, as, for example, 8 mcg. per 3 cc. of blood. We have concluded that heparin in small or moderate doses possesses a definite anticoagulant action beyond the thrombin level, since it was noted that fibrinogen was preserved in serum despite the obvious presence of thrombin. Gross coagulation of the blood specimen can not take place without thrombin. Furthermore, it is known that fresh serum contains an excess of free thrombin[19] which ought to be sufficient to coagulate the remaining fibrinogen. Although thrombin, generated during the process of coagulation, is at first kept inactive by its adsorption to fibrin[20], there is considerable clot retraction and, therefore, separation of fibrin from the thrombin containing serum during the 3 hours following gross coagulation which are required for the completion of the fibrinogen polymerization test. This freshly liberated thrombin could be expected to coagulate the remaining fibrinogen if it were not for an interference by heparin at a stage beyond the thrombin level. It has been demonstrated that the polymerization of fibrinogen is the last phase in the process of coagulation[5,8,9,22]. It succeeds the interaction of thrombin with fibrinogen and may be suppressed by

a variety of procedures. A change in pH to 5.1, as well as addition of urea or hexamethylene glycol reversibly inhibit coagulation of a fibrinogen solution, but allow thrombin to act upon the fibrinogen molecule. A proteolytic action of thrombin has been postulated at this level[22]. A peptide fragment is split off, leaving activated fibrinogen which is now prepared for polymerization provided the inhibitory factor is removed[8]. In the experiments with fibrinogen solution, restitution of a normal pH produces immediate coagulation by allowing the polymerization of fibrinogen. Since our experiments revealed an interference of heparin with the coagulation process at a point beyond the thrombin stage, it can only be concluded that heparin delays the polymerization of fibrinogen in addition to its other commonly known anticoagulant properties.

In the light of this hypothesis, the results of the present study indicate that the polymerization of fibrinogen is accelerated in patients with active rheumatic disease. This conclusion is drawn from the finding that with critical doses of heparin, such as 50 mg. injected intravenously one hour before withdrawal of blood or after the addition of 8 mcg. per 3 cc. of venous blood, no fibrinogen can be detected in serum of a specimen which has been standing in a water bath at 37° C. for 2 hours, provided it was obtained from this category of patients.

The importance of the use of critical doses of heparin is manifested by the results obtained in patients with active rheumatic disease who have received either 75 instead of 50 mg. of heparin intravenously or whose blood has been added to heparin *in vitro* observing a ratio of 12 instead of 8 mcg. to aliquots of 3 cc. The results do not mirror the activity of the rheumatoid process in either instance. The conclusion appears warranted, therefore, that the polymerization of fibrinogen in active rheumatic disease is only relatively accelerated and only to a degree which can be suppressed by a slightly larger dose of heparin, either *in vivo* or *in vitro*.

The conspicuous constancy of the finding of relatively accelerated fibrinogen polymerization in active rheumatic disease strongly indicates that the structure of the fibrinogen molecule itself may have been changed as part of the disorder. An alteration of the fibrinogen molecule in active rheumatic disease has been suggested recently by Thomas and associates[23] who found that heparin plasma obtained from 12 patients with this condition yielded a large amount of cold precipitable protein which was assumed to be closely related to fibrinogen. These authors also obtained the same finding in heparin plasma derived from rabbits in whom a generalized Shwartzman phenomenon had been produced. They assumed, therefore, that a qualitative alteration of fibrinogen may have occurred in association with the rheumatic disease. Serial studies in one of their patients, treated with salicylates and cortisone, revealed a diminution during therapy. Although their conclusion as to the qualitative alteration of the fibrinogen molecule seems to be supported by our own results, we have not been able to demonstrate any difference between the fibrinogen polymerization test before and during cortisone therapy. In particular, there was no greater trend to normalization during therapy.

The previously reached conclusion[14] that fibrinogen preservation in serum is caused by interference of heparin with fibrinogen polymerization, and not by its antithrombic properties, appears to be readily supported by the results obtained in the present study. For, if the antithrombic action of

heparin were an adequate explanation of fibrinogen preservation, a relatively larger thrombin content of blood obtained from patients with active rheumatic disease would have to be postulated after addition to heparin. Consequently, the clotting times of the heparin containing blood specimens subjected to the fibrinogen preservation test would be expected to be shorter in patients with active rheumatic disease in contrast to normal individuals or control patients. While the clotting times ranged over an extremely wide area in both groups, the mean value was 64 minutes for either category. Although no particular significance is attributed to the absolute identity of the mean clotting times, it is quite obvious that specimens of blood with clotting times varying from 30 to 120 minutes or from 31 to 120 minutes do not possess characteristic thrombin concentrations identifying each of the two categories. The fact that fibrinogen is preserved in one group after a given time interval and not in the other, must, therefore, be entirely independent of the thrombin content of the particular specimen. Consequently, the preservation of fibrinogen in serum can be explained only as the result of an inhibitory effect of heparin upon a stage of the coagulation mechanism which is beyond the thrombin level, namely, the polymerization of fibrinogen.

It also is of interest that the clotting times after addition of 8 mcg. of heparin to 3 cc. of blood were considerably longer than those ordinarily obtained with the technique of the "heparin clotting time"[12,21]. The latter procedure utilizes 4 mcg. of heparin and 1 cc. of blood. This represents a relatively higher ratio of heparin to blood, yet the clotting times are shorter. It seems, therefore, that the relative concentration of heparin may not be so significant as the absolute quantity employed.

The acute phase of disease is known to produce nonspecific changes in the blood which have been termed "acute phase reactants"[1,6,7]. Thus, acute rheumatic disease is associated with significant elevations of most serum globulins, hexosamine, nonprotein polysaccharides, mucoproteins, hyaluronidase inhibitor, C-reactive protein and plasma fibrinogen. But these alterations are also encountered in a great variety of nonrheumatic conditions including bacterial infections, malignancies or aseptic necrosis as in myocardial infarction. Fibrinogen levels are elevated in any process characterized by tissue breakdown[3]. The quantitative alterations of fibrinogen in active rheumatic disease are in no way specific but may indicate the severity of the inflammatory reaction[15,17,25]. On the other hand, the relative acceleration of fibrinogen polymerization is a phenomenon which in this series has been observed only in active rheumatic disease without being indicative of the magnitude of the rheumatic process. Moreover, the originally elevated fibrinogen concentration is suppressed during administration of cortisone, whereas the fibrinogen polymerization test appears in no way affected by the therapeutic administration of these hormones. It assumes a normal pattern only when the rheumatic process subsides.

Summary. 1. Considerable amounts of fibrinogen remain preserved in serum when heparin has been administered *in vivo* or added *in vitro* to the blood specimen.

2. This phenomenon of fibrinogen preservation in serum has been attributed to interference with fibrinogen polymerization by heparin.

3. Fibrinogen preservation in serum resulting from the use of critical doses of heparin, either 50 mg. heparin intravenously or 8 mcg./3 cc. *in vitro*, has been termed "fibrinogen polymerization

test." It is believed to differentiate between normal and accelerated fibrinogen polymerization.

4. Absence of fibrinogen in serum 2 hours after gross coagulation of heparinized blood with critical doses has been called "positive fibrinogen polymerization" and indicates an abnormal result.

5. Presence of fibrinogen in serum 2 hours after gross coagulation of blood heparinized with critical doses has been termed "negative fibrinogen polymerization" and represents a normal finding.

6. In a series of 42 patients with active rheumatic disease the fibrinogen polymerization test was "positive" in all instances. On the other hand, it was "negative" in 12 normal subjects and 21 control patients with a variety of clinical conditions.

7. The fibrinogen polymerization test was not affected by cortisone. In patients with acute rheumatic fever it remained positive long after all other laboratory criteria of activity had returned to normal.

8. The fact that clotting times of heparin containing blood derived from rheumatic and nonrheumatic individuals display almost identical values has been considered additional evidence of the previously advanced assumption that fibrinogen preservation in serum is not due to the antithrombic properties of heparin but to interference with fibrinogen polymerization.

REFERENCES

1. **Adams, F. H.:** J. Am. Med. Assn., **156**, 1319, 1954.
2. **Applezweig, N., Wald, N., Vorzimer, J.,** and **Sussman, L. N.:** Am. J. Clin. Path., **20**, 1110, 1950.
3. **Best, C. H.,** and **Taylor, N. B.:** The Physiologic Basis of Medical Practice. Baltimore: Williams & Wilkins Co., 1945, p. 4.
4. **Cantarow, A.,** and **Schepartz, B.:** Biochemistry. Philadelphia and London: W. B. Saunders Co., 1954, p. 736.
5. **Ehrlich, P., Shulman, S.,** and **Ferry, J. D.:** J. Am. Chem. Soc., **74**, 2258, 1952.
6. **Kelley, V. C.:** J. Ped., **40**, 405, 1952.
7. Idem: Ibid., **40**, 413, 1952.
8. **Laki, K.:** Blood, **8**, 845, 1953.
9. **Laki, K.,** and **Mommaerts, W. F. H. M.:** Nature, **156**, 664, 1945.
10. **Laruelle, P.:** Sang, **21**, 810, 1950.
11. **Lenggenheimer, K.:** Weitere Fortschritte in der Blutgerinnungslehre. Stuttgart: Georg Thieme Verlag, 1949, p. 223.
12. **Losner, S.,** and **Volk, B. W.:** Am. J. Med. Sci., **226**, 61, 1953.
13. Iidem: Proc. Soc. Exper. Biol. & Med., **86**, 428, 1954.
14. Iidem: Ibid., **87**, 417, 1954.
15. **Losner, S., Volk, B. W.,** and **Kanof, A.:** Am. Heart J., in press.
16. **Losner, S., Volk, B. W., Newhouse, S.,** and **Jacobi, M.:** J. Lab. & Clin. Med., **36**, 473, 1950.
17. Iidem: Ibid., **38**, 28, 1951.
18. **Quick, A. J.:** The Physiology and Pathology of Hemostasis. Philadelphia: Lea & Febiger, 1951, p. 36.
19. Idem: Ibid., p. 162.
20. **Quick, A. J.,** and **Favre-Gilly, J. E.:** Am. J. Physiol., **158**, 387, 1949.
21. **Rosenthal, R. L.:** J. Lab. & Clin. Med., **34**, 1321, 1949.
22. **Sherry, S., Troll, W.,** and **Glueck, H.:** Physiol. Rev., **34**, 736, 1954.
23. **Thomas, L., Smith, R. T.,** and **Von Korff, R.:** Proc. Soc. Exper. Biol. & Med., **86**, 813, 1954.
24. **Vinazzer, H.:** Acta med. scandinav., **142**, 468, 1952.
25. **Volk, B. W., Losner, S., Jacobi, M.,** and **Lazarus, S. S.:** Am. J. Clin. Path., **22**, 99, 1952.

THE VALUE OF PARENTERAL RESERPINE IN ACUTE HYPERTENSION*

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Two years' experience attests to the fact that *Rauwolfia serpentina* is an important addition to the therapy of hypertension. Only moderately antihypertensive, it slows the pulse, exerts a mild sedative action and is remarkably free from clinical toxicity. Used alone, Rauwolfia seems to be most effective in excitable patients with tachycardia and hypertension.

Previous reports, particularly those of Wilkins[12,13], Moyer[7], and ourselves[3] have shown: (1) Rauwolfia is definitely superior to mild barbiturate sedation for the reduction and relief of anxiety in mild hypertension. (2) When Rauwolfia is used in combination with Veratrum, hexamethonium, pentapyrollidinium or l-hydrazinophthalazine, it is possible to make significant reductions in the dosage of these more potent agents. Therefore, these more potent drugs become easier to administer and unpleasant side effects are less frequent.

Because of the favorable experience with Rauwolfia in the long-term therapy of hypertension and the preliminary reports of the therapeutic benefits of parenteral reserpine in excitable psychiatric patients[2,10], it seemed that parenteral reserpine might be a useful adjunct in the treatment of the acute hypertensive state, where sedation is still the most popular form of therapy.

Could parenteral reserpine be substituted for parenteral barbiturate therapy? Does parenteral reserpine potentiate the therapeutic action of Veratrum or Apresoline as oral reserpine does? In an attempt to answer these questions, reserpine was given parenterally to 192 patients with acute hypertension due either to toxemia of pregnancy or to essential hypertension. The results of treatment form the basis of the present report.

Methods and Materials. The subjects were patients on the obstetrical and medical wards of the District of Columbia General Hospital. One hundred sixty-two patients on the obstetrical wards received the drug intravenously, and 30 patients on the medical wards received the drug intramuscularly.

At the beginning of the study a variety of doses was tried, ranging between 2.5 mg. and 7.5 mg. It was soon found, however, that doses in excess of 2.5 mg. were no more effective; so, this dose of reserpine†

*This investigation was supported by research grants from: Irwin, Neisler & Company, Decatur, Illinois; Ciba Pharmaceutical Products, Incorporated, Summit, New Jersey; and Riker Laboratories, Incorporated, Los Angeles, California.

†Reserpine used in this study was supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

was used throughout the remainder of the study.

In all cases except those with severe toxemia, a 2-hour trial period of bed rest was given before reserpine therapy was started. If a hypotensive effect or alleviation of the toxic symptoms or both, were seen, no other therapy was instituted. Eighty-six patients received a single 2.5 mg. injection of reserpine, and in 5 patients multiple intravenous injections were given. When reserpine was repeated, it was given at 8 to 12-hour intervals.

When, after 2 hours, reserpine was found to be ineffective, or the toxemic state seemed to require more vigorous therapy, alternate patients received a synthetic product of Veratrum viride (Unitensen*) intramuscularly and the others received l-hydrazinophthalazine (Apresoline**) intravenously.

Forty-seven patients received reserpine plus Unitensen and 24 patients received reserpine plus Apresoline. Unitensen was given intramuscularly in dosage of 1 mg. mixed with 1 cc. of 1% procaine and this dose was repeated hourly if necessary to keep the blood pressure under 140/90 mm. Hg. Details of the Veratrum treatment of pregnancy have been described in detail elsewhere[6]. Twenty patients received a single 1-mg. injection of Unitensen; 14 patients required 2 injections; one required 3, and one patient required 8 injections. It was not necessary to give Veratrum intravenously during this study.

Apresoline was given intravenously in a dosage of 10 to 20 mg. and repeated as needed to keep the blood pressure under 140/90 mm. Hg. Six patients required a single 10 mg. injection; 10 patients required 2 injections; and 8 required 3 or more injections of Apresoline.

Besides the usual obstetrical examination, the blood pressure was recorded at least at half-hourly intervals and urinalyses were performed daily.

Results. The diagnoses in the 91 patients treated with reserpine alone included hypertensive vascular disease, 66; true toxemia, 20; hypertensive vascular disease and pyelonephritis, 3; hypertensive vascular disease and diabetes, 1; and, hypertensive vascular disease and toxemia, 1. The patients with hypertensive vascular disease demonstrated hypertensive retinopathy, peripheral edema was absent or at the most 1+, periorbital edema was absent and albuminuria was absent or 1+. The patients with true toxemia were characterized by a rising diastolic pressure, albuminuria, and, the best sign, a generalized retinal sheen (a wet, glistening appearance of the entire retina)[5]. The patients with hypertensive vascular disease plus superimposed toxemia all had a history of hypertension antedating their pregnancy. Examination of the retinæ, besides revealing the chronic changes of hypertension, also showed the generalized retinal sheen. Other signs of toxemia were also present: edema of the ankles and periorbital area and albuminuria. Congestive heart failure was not a feature. The diagnosis of pyelonephritis was substantiated by microscopic urinalysis, gitter cell stain and urine culture. Diabetes was diagnosed in the usual way.

In the group of nonpregnant hypertensive patients given reserpine intramuscularly, 6 patients were in the malignant phase, 3 showed grade 3 retinopathy and 21 showed either grade 1 or grade 2 retinopathy. These patients received single injections of the drug merely to ascertain if reserpine was active by the intramuscular route.

Fifteen to 20 minutes following the first injection of reserpine, there was a moderate flushing of the face which lasted about one hour. This effect diminished with each subsequent injection.

Following intravenous reserpine, there was a delay in action of at least one hour before the effect was wit-

*Unitensen used in this study was supplied by Irwin, Neisler, & Company, Decatur, Illinois.

**Apresoline used in this study was supplied by the Ciba Pharmaceutical Products, Inc., Summit, New Jersey.

nessed. By 75 minutes, a slight response was usually seen, and not until 2 to 2.5 hours following the administration of the drug was the maximum effect noted. When given intramuscularly, the onset of action was not seen before 2 hours and the maximum effect was seen 3 to 4 hours following administration. When the drug was given intravenously, the duration of response was 2 to 16 hours, with an average duration of 6.5 hours. Intramuscularly, the duration of action of reserpine was 3 to 22 hours, with an average of 9.5 hours.

Following the intravenous administration of reserpine, the systolic blood pressure fell an average of 23.5 (10 to 50) mm. Hg, and the diastolic pressure fell an average of 19.4 (10 to 80) mm. Hg. In the group of patients given reserpine intramuscularly, the response was almost identical to that seen following intravenous use. Four of the 6 patients in the malignant phase of hypertension failed to show a blood pressure reduction. When reserpine was given intravenously to these patients, a response was not observed. In the remaining 26 patients, the systolic blood pressure was reduced an average of 20 mm. Hg and the diastolic pressure was reduced an average of 19 mm. Hg.

The pulse rate showed an average reduction of 8 (0 to 15) beats per minute following intravenous or intramuscular reserpine.

More striking than the blood pressure lowering effects of parenteral reserpine was the calming influence of the drug, particularly the frequent instances of complete relief of anxiety. This tranquillizing influence became apparent 30 minutes after an intravenous injection and 45 minutes following intramuscular injection. The maximum effect corresponded with the hypotensive effect, that is, 2.5 to 5 hours following parenteral administration. Although difficult to evaluate objectively, especially on the obstetrical wards, this quieting effect of reserpine seemed to last an average of 11 to 12 hours. Excitable, tense patients would commonly be found in a normal sleep. If not spoken to or disturbed, they would remain in this state until the effects of the medication had worn off.

TOXICITY. Excessive drowsiness was noted in 6 subjects. Five patients complained of nasal congestion. In this regard, it should be noted that nasal congestion and increased tracheobronchial secretions were noted in 3 infants delivered from mothers treated with parenteral reserpine. Three patients noted loose stools for 24 hours and one patient complained of nausea while on parenteral reserpine.

In 2 subjects, 50 mg. pentobarbital sodium, given intravenously 5 hours after 2.5 mg. reserpine was given, caused profound drowsiness, bordering on coma. Repeating the same dose of pentobarbital several days later without previous reserpine caused no more than minimal sedation. A fall in blood pressure to shock levels was seen following saddle block anesthesia with procaine in 3 reserpine-treated cases. In both instances, the arterial pressure was restored promptly with intramuscular phenylephrine hydrochloride. Two hours following 2.5 mg. of reserpine given intravenously, the arterial pressure had fallen to shock levels in 2 patients. The arterial pressure was promptly restored by noradrenalin.

In order to appraise the effect of higher doses of reserpine, 15 patients were given 10 mg. intravenously. The reduction of arterial pressure in these cases was no greater than when smaller doses of reserpine were given. Ten of these patients noted increased drowsiness and 7 patients complained of nasal congestion. There were no in-

stances of mental depression or abnormal bleeding tendencies.

RESERPINE PLUS UNITENSEN. Forty-seven patients were in this group. The diagnoses included 18 patients with hypertensive vascular disease; 21 patients with true toxemia; 7 patients with hypertensive vascular disease plus superimposed toxemia; and, one patient with hypertensive vascular disease plus pyelonephritis.

The systolic blood pressure fell between 15 and 65 mm. Hg, with an average reduction of 33.2 mm., and the diastolic blood pressure fell between 10 and 45 mm. Hg, with an average reduction of 25.4 mm. The systolic blood pressure was reduced by more than 30 mm. Hg in 26 patients; between 20 and 29 mm. in 14 patients; between 10 and 19 mm. in 5 patients; and, under 10 mm. Hg in 2 patients. The diastolic blood pressure was reduced by more than 30 mm. Hg in 18 patients; between 20 and 29 mm. in 15 patients; between 11 and 19 mm. in 10 patients; and, under 10 mm. in 4 patients.

The average pulse rate during the combined therapy was 67 beats per minute. The hypotensive effect following intramuscular Veratrum began in 30 minutes and the peak of action was seen at 45 minutes. The duration of the combined hypotensive effect varied between 2 and 12 hours, with an average of 8.5 hours.

Vomiting from Veratrum was seen in 2 of the 47 cases, or 4%. There was one fetal death due to prematurity associated with severe toxemia.

RESERPINE AND APRESOLINE. Twenty-four patients were in this group. The diagnoses included 12 patients with hypertensive vascular disease; 5 patients with toxemia; 5 patients with hypertensive vascular disease plus toxemia; one patient with hypertensive vascular disease and pyelonephritis; and one patient with hypertensive vascular disease, toxemia, and pyelonephritis.

The systolic pressure was reduced more than 40 mm. Hg in 10 patients and between 20 and 39 mm. Hg in 14 patients. The diastolic pressure was reduced more than 40 mm. Hg in 7 patients, between 20 and 39 mm. in 14 patients, and under 3 mm. in one patient.

The systolic blood pressure was reduced between 15 and 70 mm. Hg, with an average reduction of 36.5 mm., and the diastolic blood pressure was reduced between 10 and 80 mm. Hg, with an average reduction of 30.2 mm. The average pulse rate during therapy varied between 80 and 115 beats per minute, with an average of 95 beats per minute.

The hypotensive response from Apresoline began to show its effect 10 to 15 minutes after injection; the maximum effect was seen in 20 minutes. The duration of action of the combined therapy varied between 3 and 14 hours, with an average duration of 7.5 hours.

Following Apresoline, vomiting was seen in 3 patients, headache in 2 and chills in one.

Discussion. It is seen from our data that parenteral reserpine alone was not effective in all cases, since 44% of cases, or 71 of the 162 treated cases, required the addition of Veratrum or Apresoline to bring about a satisfactory hypotensive response. Since reserpine takes 1.5 to 2.5 hours to exert its maximum effect when given intravenously (3 to 4 hours when given intramuscularly), it should obviously not be relied on as the sole form of therapy in severe toxemia, particularly in eclampsia. Furthermore, because of the reserpine's property of potentiating the sedative action of barbiturates in some patients, it would seem advisable not to administer the two drugs concomitantly.

In mild to moderate toxemia or in acute hypertension, however, after bed rest has been tried and found unsuccessful, 2.5 mg. reserpine given parenterally seems to be the treatment of choice. Besides the significant hypotensive effect in more than half of the cases, its ability to alleviate anxiety and to calm the tense patient without causing coma or unconsciousness, makes the drug a most useful agent. Indeed, if parenteral reserpine had no hypotensive effect at all, it would still be an important therapeutic advance.

The ability of Veratrum to lower blood pressure and slow the pulse, particularly in toxemia of pregnancy, has never been doubted. The only drawback to wide acceptance of the drug has been the relatively narrow margin between the dose required for hypotension and that causing nausea and vomiting.

Previous experience in this clinic with over 1000 cases treated with intramuscular Veratrum has shown the incidence of vomiting to be 16%[4]. When reserpine was used as background therapy for Veratrum in the present study, the incidence of vomiting was only 5%. When given alone, the incidence of vomiting following Veratrum was greatest when the drug was given intravenously, occurring in from 65 to 75% of cases. When given intramuscularly, the incidence was proportional to the amount and frequency that Veratrum was administered; the more Veratrum given, the more vomiting. Using combined therapy, it was necessary to give Veratrum intravenously only once.

Though reserpine did not significantly enhance the hypotensive effect of Veratrum, it more than doubled the duration of response. The duration of hypotension from intramuscular Veratrum alone averaged 3.5 hours. The duration of hypotension in our reserpine plus Veratrum-treated cases averaged 8.5 hours.

No claim of simplicity can be attached to Veratrum given intravenously. Tachyphylaxis (a temporary refractory period) occurs in 25 to 35% of cases and vomiting occurs in 40%[6]. Used as background therapy, reserpine essentially does away with the need for intravenous Veratrum, thus bypassing most of the difficulties associated with Veratrum therapy.

It is seen then that when reserpine is added to Veratrum, the duration of action is doubled, permitting less Veratrum to be used, thus making Veratrum easier to administer, more effective and less toxic. The tranquillizing effect of reserpine plus the hypotensive effect of Veratrum makes for a particularly effective combination.

In similar fashion, reserpine was found to enhance the hypotensive effect and prolong the action of Apresoline, permitting the use of smaller doses of the drug which significantly reduced side effects. Previous experience in this hospital[4] using 30 mg. Apresoline intravenously revealed an average of 25 mm. Hg reduction in diastolic pressure in 30 hypertensive patients and an average diastolic reduction of 40 mm. Hg in 25 toxemic patients. The average duration of hypotension in these cases was 4.5 hours. Using the same dosage, Assali and Suyemoto[1], and Kistner[9] found similar reductions in arterial pressure; greater reductions in pressure being found in toxemia patients.

In our reserpine plus Apresoline-treated cases, using only 10 to 20 mg. intravenously, the diastolic pressure fell an average of 30 mm. Hg and the duration of hypotension averaged 7.5 hours. Others[11] and ourselves[8] have

found tachycardia (more than 110 beats/min.), a sensation of fullness, throbbing of the head and particularly headache to be frequent side effects of parenteral Apresoline. It is noteworthy, therefore, that 18 of our 24 Apresoline plus reserpine-treated patients showed no side effects.

Experience thus far suggests that all that can be said about the use of oral Rauwolfia in chronic essential hypertension may be duplicated for the use of parenteral reserpine in acute hypertension. Used alone, parenteral reserpine has a moderate hypotensive and bradycrotic effect. It relieves anxiety and irritability and calms the patient so effectively that because of this latter property alone, the drug should remain in the medicinal armamentarium. As a hypotensive agent and a tranquillizer, parenteral reserpine (as with oral reserpine) does a better job than the barbiturates, without any of their unpleasant side effects. Tolerance has not been noted and side effects, except for occasional drowsiness, have been absent.

Again, as with Rauwolfia given orally, the greatest usefulness of the drug given parenterally is with the more potent (and toxic) hypotensive agents where it is used as a background agent, making these latter drugs more effective, less toxic and easier to adminster.

Our more recent experience, and the experience of others[2,10], suggests that intramuscular reserpine is as effective as when given intravenously. For practical purposes, this eliminates the need for intravenous drug therapy in acute hypertension: a definite advantage indeed. A rational plan of therapy for acute hypertension in the moderately sick patient should include:

1) 2.5 mg. reserpine intramuscularly to be repeated every 12 hours.
2) If no hypotensive effect in 2 hours, or if any worsening of the clinical state should occur, give 0.5 mg. purified Veratrum intramuscularly.

In the severely ill patient with acute hypertension, reserpine and Veratrum or Apresoline should be administered at once, preferably in the same syringe. If no effect from combined intramuscular therapy is witnessed, then intravenous Veratrum or Apresoline therapy is indicated.

Summary. Parenteral reserpine was given to 162 hospitalized hypertensive and toxemic patients. Ninety-one patients showed an average reduction of 23 mm. Hg in systolic pressure and 19 mm. Hg diastolic pressure, an effect which lasted an average of 6.5 hours. More striking than the hypotensive effect was the calming influence of the drug, with frequent complete relief of anxiety.

As with oral reserpine, the greatest use of the drug given parenterally was as background therapy to the more potent hypotensive agents. Though Veratrum or Apresoline was needed to reduce the arterial pressure and control the toxemic state in 71 patients, reserpine enhanced and prolonged the action of these more potent drugs, reduced the dosage requirement, thus greatly reducing the toxicity and making these potent agents much easier to administer.

REFERENCES

1. **Assali, N. S.,** and **Suyemoto, R.:** Am. J. Obst. & Gynec., **64**, 1021, 1952.
2. **Barsa, J. A.,** and **Kline, N. S.:** Unpublished data.

3. **Finnerty, F. A., Jr.:** Am. J. Med., **27, 629, 1954.**
4. Idem: Unpublished data.
5. Idem: J. Am. Med. Assn., **154,** 1075, 1954.
6. **Finnerty, F. A., Jr.,** and **Fuchs, G. J.:** Am. J. Obst. & Gynec., **66,** 830, 1953.
7. **Ford, R. V.,** and **Moyer, J. H.:** G. P., **8,** 51, 1953.
8. **Freis, E. D.,** and **Finnerty, F. A., Jr.:** Proc. Soc. Exper. Biol. & Med., **75,** 23, 1950.
9. **Kistner, R. W.:** J. Obst. & Gynec. Brit. Emp., **61,** 463, 1954.
10. **Noce, R. H., Williams, D. B.,** and **Rapaport, W.:** J. Am. Med. Assn., **156,** 821, 1954.
11. **Sellers, A. M.,** and **Hafkenschiel, J. H.:** Am. J. Med. Sci., **228,** 114, 1954.
12. **Wilkins, R. W.:** Am. J. Med., **27,** 703, 1954.
13. **Wilkins, R. W.,** and **Judson, W. E.** New England J. Med., **248,** 48, 1953.

THE POSSIBLE THERAPEUTIC VALUE OF CHOLECYSTECTOMY IN ADAMS-STOKES DISEASE

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There has long been more than a suspicion that some relationship exists between the gallbladder and the heart[1,5,10]. Physiologists have noted a reflex mechanism from the former to the latter[6]. Clinicians have tried to correlate certain cardiac arrhythmias with the gallbladder. Transient auricular fibrillation, particularly, has been thought to have this mechanism in some instances[3]. Furthermore, anginal pain in some patients has been thought to develop as a result of a trigger mechanism coming from a diseased gallbladder.

Buchbinder, in 1929[2], produced either a sinus bradycardia or asystole in frogs by sudden alteration of pressure in the gallbladder. He was able to abolish this reflex by atropine or by cutting the vagus, and concluded that it was a vagal reflex. Owen, in 1933[8], distended the biliary tract in 5 jaundiced unanesthetized dogs and produced ectopic auricular beats or heart block in 3 dogs and suggested that icterus "sensitizes the heart" to the vagal mechanism. Newman[7] observed sinus arrhythmias, occasional "T" wave inversions and extrasystoles in "spastic distention" of the gallbladder. Gilbert[4] produced a variety of arrhythmias in dogs by distending the gallbladder and other abdominal viscera. A case of diverticulum of the esophagus was thoroughly studied by Weiss and Ferris[9] in which distention of the diverticulum by a balloon reproduced syncopal attacks due to the development of temporary partial heart block.

From an experimental and clinical point of view, it is therefore apparent that the gallbladder may play a role in some disturbances of cardiac mechanism. With this in mind, a small series of cases with complete heart block, particularly those with Adams-Stokes attacks who also had gallbladder disease were investigated. One case (No. 3) did not have Adams-Stokes attacks according to the strict definition of the term, but had very similar syncopal episodes associated with first degree heart block and sinus pauses.

When a patient has complete heart block with a fairly steady, slow ventricular rate, he may continue in good health for weeks, months or years and suddenly, without apparent cause, become unconscious for seconds or minutes quickly returning to his former

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state of health. The structural state of the heart most likely remains essentially unchanged. The transient nature of the whole episode is too sudden and fleeting to be caused by a new anatomical injury. It is more logical to assume that such a spell is neurogenic in origin, possibly as a result of temporary vasospasm. If reflexes from a pathological abdominal viscus could produce such alterations in the heart, it seems not illogical that gallstones, or the accompanying cholecystitis might in some measure act in this way and be partly responsible for syncopal attacks in cases of complete heart block.

This report describes experiences with 7 patients, 5 of whom had typical attacks of Adams-Stokes syncope. All 7 had gallstones, and in each a successful cholecystectomy was performed. Biliary symptoms were present in the preceding year in every instance, and all but 2 showed electrocardiographic evidence of complete heart block preoperatively. One of the latter was the patient having first degree block and sinus pauses, and the other had had an electrocardiogram, taken sometime before admission, which showed transient complete heart block during a spell. The pertinent data on these cases are shown in Table 1. The ages ranged from 47 to 72 years. There were 4 men and 3 women.

Of these 7 cases, one was possibly congenital in origin, one may have been the result of diphtheria in childhood, and the other 5 were due to arteriosclerosis of the coronary arteries or hypertension. They all had one form or another of general anesthesia, all but one being given ether. The preoperative medication in all instances was the subcutaneous administration of 0.6 mg. atropine sulfate and 10 mg. morphine sulfate, with the exception of Case No. 6, who received only Nembutal 100 mg. by mouth. Inasmuch as this series of cases is a small one, brief summaries of those patients having syncopal attacks are presented.

Case Histories. CASE 1, A.F. PBBH #8B582, a 48-year-old married factory foreman had had Adams-Stokes attacks and angina pectoris for 7 years, during which time he had had known complete heart block. For 2 years he had had infrequent attacks of burning epigastric pain unrelated to meals. One month prior to entry, he experienced a severe episode of right upper abdominal pain radiating to the back, with nausea and vomiting. At this time he also had a most pronounced syncopal attack. There was no history of rheumatic fever, myocardial infarction, diphtheria, or hypertension. Physical examination showed a pulse of 34, blood pressure of 115/40, slight enlargement of the heart, no murmurs but a changing intensity of the first heart sound. Electrocardiogram revealed right bundle branch block, a ventricular rate of 29, and an auricular rate of 100. Roentgenographic examination showed a generally enlarged heart without calcification, and a poorly functioning gallbladder. Cholecystectomy under avertin-ether was performed Sept. 8, 1942, without complication other than some difficulty with respiration initially. At follow-up 9 years later in 1951, he was found to be working, and generally improved. There had been only one episode of unconsciousness. There was no sign of congestive failure. Examination of the heart was essentially unchanged and the electrocardiogram was the same. He was last seen February 24, 1954, and was well, taking Isuprel, having no attacks of syncope or even dizziness. The physical examination and electrocardiogram were unchanged.

CASE 2, L.C. PBBH #G-5154, a 54-year-old white housewife had had general weakness for 3 years, hypertension (250 systolic) for 2 years with associated angina pectoris, no known myocardial infarction. Four months previous to admission, she first experienced right upper quadrant pain with several mild episodes subsequently. Two months later, she had the first Adams-Stokes attack and 2 such episodes thereafter, the last one a week prior to admission. She had no history of rheumatic fever or diphtheria. Physical examination showed: pulse 38, blood pressure 180/80. There was a grade 1 apical and aortic systolic murmur, but no change in first heart sound. The heart was considerably enlarged. The electrocardiogram showed 2nd degree heart block (2:1), left ventricular

TABLE 1.—PERTINENT DATA IN 7 PATIENTS

Case	*Age*	*Sex*	*Etiology of Heart Disease*	*ECG*	*Vent. Rate*	*Operation*			*Number of Attacks Before–After*	*Length Follow-up*
						Date	*Duration (min.)*	*Anesthetic*		
1. A.F.	48	M	? CAD	Complete A/V block, RBBB	34	9/ 8/42	120	Avertin, ether	3/yr.—1/12 yrs.	12 yrs.
2. L.C.*	54	F	? CAD HCVD	2nd deg. block (2–1), LVH	38	4/19/46	70	Ether	3/2 mo.—0/2 yrs.	7 yrs.
3. C.D.*	72	F	HCVD CAD	1st deg. block, sin. bradycardia and LVH	42	8/ 7/46	45	Avertin, GOE	24/yr.—2/yr.	2 yrs.
4. G.D.	70	M	? CAD	RBBB	80	9/17/47	60	Ether	1/wk.—0/9 mo.	9 mo.
5. C.S.	53	M	? Diphtheria ? CAD	2nd deg. to comp. A/V block, RBBB	42	5/24/49	50	Local, ether	4/mo.—1/4 yrs.	4 yrs.
6. J.G.	65	F	? CAD	Complete A/V bl. Low EMF, in RBBB	40	7/ 6/54	50	Succinylcholine N_2O, curare	4/day—0/6 mo.	6 mo.
7. J.M.	47	F	? Congenital	Complete A/V bl. Auric. fibril.	47	6/ 5/44	140	Ether	0 0	6 mo.

* Deceased; CAD, coronary artery disease; A/V, auriculo-ventricular; RBBB, right bundle branch block; HCVD, hypertensive cardiovascular disease; LVH, left ventricular hypertrophy; EMF, electro-motive force; GOE, gas-oxygen-ether.

hypertrophy, ventricular rate 38; roentgenograms showed 15% cardiac enlargement, but no calcification. The gallbladder film revealed numerous positive calculi. Cholecystectomy was performed April 18, 1946, under ether anesthesia, without incident or postoperative complications. Follow-up observation showed considerable improvement, the patient going without attacks of syncope for 2 years. She then developed a nervous breakdown, had a return of heart block, and only one episode of syncope 2½ years postoperatively. She then had gradual increase in invalidism over the next 5 years and increasing auricular-ventricular block until it was complete, whereupon there were more attacks of syncope. The electrocardiogram taken during one episode, April 1, 1953, showed ventricular tachycardia, and the patient expired during an attack. Necropsy showed extensive generalized arteriosclerosis, particularly of the coronary arteries, but no area of infarction.

CASE 3, C.D. PBBH #R-1667, a 72-year-old white single woman had had diabetes mellitus and hypertension for many years. For at least 5 years she had had Adams-Stokes attacks of gradually increasing severity from every 3 to 4 months, to 3 or 4 a month, often associated with attacks of right upper quadrant pain, and gaseousness after meals. She had had angina pectoris of moderate severity for several years but no known myocardial infarction and no history of rheumatic fever or diphtheria. Physical examination revealed a pulse of 50, blood pressure of 175/65, a generally enlarged heart without a changing first sound. Electrocardiogram showed first degree block, rate of 42, and left axis deviation. Tracings during attacks showed asystole of several seconds or more. Cholecystogram revealed a nonfunctioning gallbladder with opaque stones. Cholecystectomy was performed August 7, 1946, under avertin-ether anesthesia without complication. For about one year she was definitely improved with a reduction in number of attacks to about one every 5 or 6 months although she had some episodes of dizziness. Following this, however, she gradually noted increase in anginal pain, developed congestive heart failure, had at least 2 myocardial infarctions, and died in a nursing home January 1, 1950. At necropsy, severe coronary artery disease was noted, with complete occlusion of the anterior descending coronary artery.

CASE 4, G.D. PBBH #5A905, a 70-year-old white male physician had had Adams-Stokes attacks for 5 years on the basis of presumed coronary artery disease without angina or known myocardial infarction, with right bundle branch block and transient complete auriculo-ventricular block. The attacks were noted to occur more often after meals consisting of fatty and fried foods. Two episodes of right upper quadrant pain and fever occurred within 6 weeks of entry with increase of syncopal attacks to 3 to 4 a day, at least once a week. There was no history of rheumatic fever, diphtheria, or hypertension. Physical examination showed a well preserved, elderly male, heart regular at 80, blood pressure 134/86, two plus apical systolic and one plus aortic systolic murmurs, and no sign of congestive failure. Roentgenogram revealed a normal heart in size and configuration with calcification noted only in the arch of the aorta. Cholecystogram showed several positive calculi and poor function. Cholecystectomy was performed on September 17, 1947, under nitrous oxide-oxygen-ether anesthesia with one episode of asystole lasting about one minute before the incision. One half cc. of epinephrine was given intramuscularly and the heart beat resumed spontaneously. Except for a mild febrile episode, the postoperative course was uneventful, and at a 9-month follow-up, the patient had not had an episode of unconsciousness since the operation. His only complaints were mild indigestion relieved by belladonna, and occasional spells of "giddiness" only about every 2 weeks. When last heard from, however, March 16, 1949, the patient had been admitted to Worcester (Mass.) Memorial Hospital with more attacks of syncope.

CASE 5, C.S. PBBH #5B143, a 53-year-old physician had had severe diphtheria in childhood but was otherwise well except for mild indigestion and "pylorospasm" until one year prior to entry, when he first noted angina pectoris. There was no history of rheumatic fever, hypertension, or known infarction. Two months before admission, he had a syncopal attack diagnosed as Adams-Stokes disease. At about this same time, there was an increase in severity of the indigestion, and intermittent right upper quadrant pain was experienced, associated with nausea and vomiting. The syncopal attacks increased in number and severity and were thought to be related to the abdominal pain. The physical examination showed a pulse of 42, blood pressure of 140/80, no change in first heart sound, although auricular sounds were heard. There was tenderness in the right upper quadrant. The electrocardiogram showed right bundle branch block, intermittent second degree block (2:1) alternating with a normal sinus rhythm. Roentgenograms of the heart were normal; no calcification was seen. Calculi

were noted in the gallbladder. First attempt at cholecystectomy, May 16, 1949, under nitrous oxide-ether anesthesia was unsuccessful due to 4 episodes of asystole prior to incision. Intracardiac epinephrin was required twice, and just stimulating the ventricle by a needle sufficed to restore the heart beat the other 2 times. The operation was finally carried out successfully, May 24, 1949, under local anesthesia, although there were several periods of asystole again requiring intracardiac epinephrin; the postoperative course was uneventful. Follow-up observation 4 years later showed him to be generally improved and working, having had only one attack of syncope.

CASE 6, J.G. PBBH #K5590, a 65-year-old white woman had had mild diabetes mellitus for 16 years and probable angina pectoris for 3 years without known myocardial infarction. Complete heart block was noted for one year after onset of typical Adams-Stokes attacks of syncope, at first occasional and mild, but recently severe and up to 4 a day. There was no history of rheumatic fever, diphtheria, or hypertension. Intermittent right upper quadrant pain, nonradiating, had been noted for 1 to 2 years. The physical examination revealed a pulse of 40, blood pressure 150/70. The first heart sound at apex varied in intensity. Grade 2 systolic murmur at the aortic area transmitted to the neck, with a good split aortic second sound and moderate right upper quadrant tenderness were present. Roentgenogram showed the heart to be 22% enlarged to right and left, and a cholecystogram demonstrated a single gallstone 5 cm. in diameter. Because of a suspected relationship between attacks of right upper quadrant pain to Adams-Stokes attacks and angina, cholecystectomy was performed July 6, 1954, under nitrous oxide and succinyl choline anesthesia. Six episodes of asystole occurred during the procedure as detected by the electrocardiograph, each being corrected by manual stimulation through the diaphragm, or by moderate pounding of the precordium. Intracardiac epinephrine, or cardiac massage was not necessary. Postoperative course was uneventful except for 3 mild syncopal episodes up to the 6th postoperative day, since which time she has had no syncopal episode and has felt fairly well over a 6-month period.

Discussion. It is difficult to judge the value of therapy in the condition under discussion, because attacks of syncope often come in unpredictable fashion. It would appear, however, that in each instance the number of attacks of syncope was definitely decreased as a result of the cholecystectomy. The frequency of attacks before and after operation is charted in Table 1. In some, improvement seemed dramatic. In none was the cardiac condition worse as a result of the operation. The purpose and hope to be derived from the operation was a decrease in the syncopal attacks by obviating a trigger-like mechanism from a pathological gallbladder.

There obviously was apprehension concerning the operation itself for fear of a fatal attack of asystole during anesthesia. In fact, in one instance, repeated episodes of prolonged asystoles did occur during the induction of anesthesia before the operation had begun. This necessitated postponing surgery, though during the height of the second operation, 7 prolonged attacks of asystole each lasting 2 to 3 minutes and documented by electrocardiographic recordings took place. During the first 3 of these episodes intracardiac epinephrine was injected, but during the remaining 4, the surgeon (Dr. Francis D. Moore) pricked the heart with a needle thereby reinstituting cardiac contractions. This patient, a physician, has had a most gratifying result and has been back to duty for several years following the operation. There were two other instances in which asystoles occurred during operations, but who went through a successful cholecystectomy.

There were other instances where the postoperative improvement seemed too striking to be considered coincidental. Case 1 was the foreman of an electric plant who had 3 major spells during the year before operation and who in the subsequent 12 years had only one attack of unconsciousness. He was able to carry on his full duties until he reached the age of re-

tirement and has been leading a comfortable life. In another case (No. 6), there were no spells at all for the 6-month follow-up period, whereas before the operation this patient was having 4 attacks daily.

Only 2 of the 7 patients have died since the operation, 2 and 7 years postoperatively, both of cardiac disease. The other 5 were alive when last examined, the follow-up period varying from 6 months to 12 years. It is impossible to draw any inference as to the effect of operation in these cases on duration of life, though there is no reason to think that it shortened their lives.

The general impression gained in analyzing these cases is that cholecystectomy is tolerated satisfactorily by patients with complete heart block despite the occasional occurrence of asystoles during the anesthesia. Furthermore, it would appear that the possible presence of gallstones should be searched for carefully in all cases of Adams-Stokes disease and if definite stones or a pathological gallbladder are found, cholecystectomy may decrease the frequency of recurrent syncopal attacks.

Summary. Six patients with Adams-Stokes syndrome and one patient with complete heart block without syncopal attacks underwent cholecystectomy for gallstones. There was no operative mortality though 3 had attacks of asystole during anesthesia. In each case, the incidence of attacks of syncope was decidedly decreased during the postoperative follow-up period. In 4 cases the improvement was very striking. It would appear that the removal of a diseased gallbladder may not only relieve the patient of biliary symptoms, but improve the cardiac status in selected cases of complete heart block that have attacks of Adams-Stokes syncope.

REFERENCES

1. **Breyfogle, H. S.:** J. Am. Med. Assn., **114,** 1434, 1940.
2. **Buchbinder, W. C.:** Proc. Soc. Exper. Biol. & Med., **27,** 542, 1929–30.
3. **Felderbaum, D.,** and **Finesilver, B.:** Am. Heart J., **2,** 416, 1927.
4. **Gilbert, N. C., Fenn, G. K.,** and **LeRoy, G. V.:** J. Am. Med. Assn., **115,** 1962, 1940.
5. **Gueneau de Mussy,** quoted by **Revillont:** Gaz. de Hop., p. 666, 1878; cited by **Schwartz, M.,** and **Herman, A.:** Ann. Int. Med., **4,** 783, 1931.
6. **Ivy, A. C.:** J. Am. Med. Assn., **95,** 1068, 1930.
7. **Newman, C.:** Lancet, **1,** 841, 1933.
8. **Owen, S. E.:** Am. Heart J., **8,** 496, 1933.
9. **Weiss, S.,** and **Ferris, E. B.:** A.M.A. Arch. Int. Med., **54,** 931, 1934.
10. **Wolferth, C. C.:** J. Mt. Sinai Hosp., **8,** 1121, 1941–42.

THE EFFECTS OF AN ADRENERGIC BLOCKING AGENT, REGITINE, UPON THE GLUCOSE TOLERANCE CURVE IN PEPTIC ULCER PATIENTS

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Attempts to correlate peptic ulcers with derangements in the hypothalamic-pituitary-adrenal axis have been abundant, since Cushing[5] called attention, in 1932, to the relation of peptic ulcers to the "interbrain." Sandweiss[20] has long believed that hormonal factors were of prime importance in producing peptic ulcers, and concluded that a state of adrenal exhaustion, secondary to prolonged chronic stress, could be demonstrated. The appearance of peptic ulcers in patients receiving adrenal corticosteroids for other diseases is well known[15]. Mirsky *et al.*[18] demonstrated increased uropepsin excretion in duodenal ulcer patients, and Gray[10], by measuring uropepsin excretion levels after the administration of ACTH or cortisone, has shown the reality of a pituitary-adrenal pathway stimulating the secretion of gastric acid and pepsin, one which is unaffected by vagotomy or subtotal gastric resection.

Study of the carbohydrate metabolism in patients with peptic ulcers by means of the oral glucose tolerance curve has shown an abnormality consisting of a hyperglycemic rise above the expected normal, followed by a delayed drop to hypoglycemic levels[14]. In 1949, Platt[19] reported intravenous glucose tolerance tests on 15 ulcer patients and an equal number of controls, and found that the hyperglycemic peak was essentially the same in both groups, but the ulcer patients' curves descended at a slower rate and reached hypoglycemic levels lower than those of the controls.

The effect of endogenous and exogenous adrenalin on glycogenolysis with resultant rise in blood sugar is well known[2]. The role of adrenalin in activating the hypothalamic-pituitary-adrenal response is thought by some to be insignificant[16], but one of the most prompt responses to stress, evidenced even in the absence of the pituitary, is an adrenalin-mediated mobilization of glycogen stores[24]. Further, it has been shown that both oral and intravenous glucose modify the adrenal response to stress by decreasing its need of glycogenolysis catalyzed by corticosteroids[23]. Thus, as Engel has said, "it may well be that an increased need for carbohydrate is the first effect of stress in general"[8].

Whether the abnormality in the carbohydrate metabolism of ulcer patients could be linked to the adrenal stress syndrome was the subject of this investigation, a study of the effect of an adrenergic blocking agent, Regitine*, on the glucose tolerance curves of pep-

*Regitine kindly furnished by Ciba Pharmaceutical Products, Summit, N. J.

tic ulcer patients and normal individuals.

Material and Method. Four-hour *intravenous* glucose tolerance tests were performed on 11 peptic ulcer patients and 9 individuals used as controls in the following manner: a fasting blood sample was drawn and 25 gm. of glucose in 50 cc. of sterile water was injected slowly into an antecubital vein over a period of 2 minutes. Blood sugars were then obtained at intervals of 5, 15, 30 and 45 minutes, and at 1, 2, 3 and 4 hours thereafter. Pulse and blood pressure measurements were recorded during the test. One per cent Novocain was used as a local anesthetic. The patients were ambulatory but remained in the same room throughout the test. An effort was made to avoid excitement. The controls, chiefly members of the house staff, performed their usual duties.

All of the individuals were encouraged to eat carbohydrates liberally for 2 days before the test, but no strict control of diet was possible.

Subsequently, at intervals of from 24 hours to 6 months, the test was repeated following the oral ingestion of 100 mg. of Regitine 30 minutes before the test. No other modification was made.

The blood sugar determinations were made by the method of Folin and Wu (modified) with photoelectric evaluation of end points. Photoelectric apparatus was calibrated on standard solutions of the College of American Pathologists[9].

Results and Discussion. Distribution of the patients according to age, sex, race, diagnosis and duration of symptoms is given in Table 1. The average age of the ulcer patients was 41 years; of the controls, 32 years. The duration of ulcer symptoms was from one week to 30 years. There were 8 male and 3 female patients, and 9 male controls.

TABLE 1.—DISTRIBUTION OF PEPTIC ULCER PATIENTS ACCORDING TO AGE, SEX, RACE, DIAGNOSIS, AND DURATION OF SYMPTOMS

Patient	*Age*	*Sex*	*Race*	*Diagnosis*	*Duration of Symptoms*
N. F.	39	F	B	Bleeding duodenal ulcer	1 week
M. D.	47	F	W	Bleeding duodenal ulcer	3 years
M. L.	30	M	W	Duodenal ulcer	1 year
H. H.	51	M	W	Bleeding duodenal ulcer	3 weeks
J. C.	23	M	B	Duodenal ulcer	6 years
G. W.	36	M	W	Bleeding duodenal ulcer	2 years
A. P.	52	M	W	Duodenal ulcer	9 years
O. C.	33	M	W	Bleeding duodenal ulcer	1 year
J. W.	40	M	W	Bleeding duodenal ulcer	3 years
L. McQ.	66	M	W	Bleeding duodenal ulcer	30 years
H. C.	33	F	W	Duodenal ulcer	2 years
Average	*41*				
Controls					
F. B.	73	M	W	Coronary atherosclerosis	
J. C.	15	M	W		
H. C.	26	M	W		
W. K.	33	M	Y		
W. H.	27	M	W		
P. P.	26	M	W		
G. Z.	27	M	W		
V. T.	25	M	W		
H. C.	33	M	W		
Average	*32*				

Values for the glucose determinations for both ulcer patients and controls before and after Regitine are shown in Table 2. From the italicized averages it can be seen that the average fasting blood sugar value for the ulcer patients was 93 mg.; for the controls, 99 mg. per 100 cc. The glucose determinations 5 minutes after the intravenous injection of 25 gm. of glucose were

slightly higher in the controls, averaging 262 mg., while the ulcer patients' average was 253 mg. per 100 cc. Thereafter the average blood glucose values for the ulcer patients descended at a slightly slower rate than did those of the controls, and at the end of 3 to 4 hours were below the average for the controls, and also their original fasting levels.

After Regitine, there was a slight tendency towards hyperglycemia in both ulcer patients and controls, the average glucose value for the ulcer patients 5 minutes after the injection of glucose being 268 mg., while among the controls the average value was 274 mg. per 100 cc. Thereafter, this slight hyperglycemia persisted in both patients and controls, the values for the average glucose determinations remaining higher in the ulcer patients than in the controls, and higher in both than in either before Regitine. Fasting blood glucose levels were reached again by the end of 2 hours.

Blood pressure and pulse readings taken during the tests before and after Regitine showed variable hypotension and acceleration of pulse rate after Regitine. In addition, all patients noted some degree of nasal congestion, usually maximal after 2 hours and disappearing by the end of 6 hours. Two patients experienced mild syncope and 3 controls observed weakness, malaise, dizziness, nausea and dyspnea.

With the variability of intestinal motility and absorption rates, *oral* glucose tolerance curves cannot be taken as reliable indices of deranged carbohydrate metabolism in patients with peptic ulcers. So-called alimentary hypoglycemia as a part of the "dumping syndrome" seen post-gastrectomy has been shown to be related primarily to the route of glucose administration, intravenous tolerance curves being within normal limits, while the oral curves showed varying degrees of hyperglycemia with subsequent hypoglycemia[21]. The intravenous glucose tolerance curve is subject to variations, as seen in carbohydrate deprivation[17], following the administration of adrenal cortical hormones[3], and as a result of the stress accompanying illness[3]. In this study, no significant abnormality accompanied the glucose tolerance tests in the peptic ulcer patients, a finding opposed to the results of others[19].

The effect of Regitine upon carbohydrate metabolism is not clearly understood, nor is it constant; reportedly, both hypoglycemia and hyperglycemia follow its use[11,25]. Other sympathetic blocking agents, hexamethonium and dihydroergotamine, have been shown by some[13] to potentiate insulin-induced hypoglycemia, but by others[1,12] not to decrease spontaneous recovery therefrom. The role of glucagon in this regard has been presumed, since its hyperglycemic action is not blocked by dihydroergotamine[7]. Indeed, glucagon has been shown to potentiate the diabetogenic action of such agents as growth hormone, cortisone and ACTH[4], and its effect on the liver is similar to that of adrenalin[6].

No proof that adrenalin operates in an abnormality of carbohydrate metabolism in peptic ulcer patients could be demonstrated by this investigation, since the reported abnormality failed to occur. That adrenalin has a role in peptic ulcer production, however, has been suggested recently by Shay *et al.*[22], who studied gastric acidity during insulin hypoglycemia with and without Regitine block, in 5 ulcer patients. The hypoglycemia was not consistently altered by the Regitine, but the late phase of acid secretory response was definitely blocked.

The slight hyperglycemia produced by Regitine in the ulcer patients and

TABLE 2.—BLOOD GLUCOSE DETERMINATIONS IN MG. PER 100 CC. FOR PEPTIC ULCER PATIENTS AND CONTROLS, BEFORE AND AFTER REGITINE

	Before Regitine									*After Regitine*								
Patient	*F*	*5-Min.*	*15-Min.*	*30-Min.*	*45-Min.*	*1-Hr.*	*2-Hr.*	*3-Hr.*	*4-Hr.*	*F*	*5-Min.*	*15-Min.*	*30-Min.*	*45-Min.*	*1-Hr.*	*2 Hr.*	*3-Hr.*	*4-Hr.*
N. F.	92	356	214	137	108	94	89	94	92	92	304	192	127	106	94	84	87	92
M. D.	121	233	233	210	197	168	100	65	77	137	*	374	233	220	192	124	106	89
M. L.	87	227	214	192	165	156	108	72	75	82	233	187	*	100	118	97	89	84
H. H.	92	268	187	156	115	106	97	89	103	87	233	178	156	124	106	75	75	77
J. C.	84	208	187	148	118	106	82	84	84	90	227	187	160	127	118	80	77	92
G. W.	76	190	158	143	139	125	67	81	84	92	257	211	190	163	135	86	81	84
A. P.	89	195	185	154	125	103	71	84	84	86	300	235	185	158	146	69	62	69
O. C.	94	264	190	143	109	92	76	79	79	103	278	216	176	143	128	94	94	106
J. W.	106	308	229	180	132	118	100	109	100	106	286	216	180	154	118	84	92	100
L. McQ.	89	229	200	158	121	115	81	81	94	79	250	211	185	167	154	92	86	71
H. C.	94	308	242	167	150	125	73	89	94	89	308	250	190	146	125	*	81	92
Average	*93*	*253*	*204*	*164*	*135*	*119*	*86*	*84*	*88*	*95*	*268*	*223*	*178*	*146*	*130*	*89*	*85*	*87*
Controls																		
F. B.	98	283	234	192	178	152	98	104	84	106	300	235	180	171	139	100	103	106
J. C.	92	292	154	118	92	92	81	73	86	94	316	195	109	89	92	94	92	97
H. C.	89	270	250	190	163	125	67	79	89	94	326	205	200	180	167	94	79	92
W. K.	132	278	171	143	121	94	*	86	89	106	250	195	143	138	106	89	94	118
W. H.	100	250	229	185	158	128	84	84	97	106	286	216	163	125	112	94	100	103
P. P.	97	250	200	139	112	94	81	89	97	100	242	195	143	115	97	100	100	103
G. Z.	97	270	*	135	92	71	86	*	97	97	250	216	163	125	106	73	84	89
V. T.	94	211	154	103	76	71	89	89	94	92	200	176	163	125	118	*	*	*
H. C.	94	255	229	185	171	146	81	89	97	103	292	242	211	185	176	*	*	*
Average	*99*	*262*	*203*	*155*	*129*	*108*	*83*	*87*	*92*	*100*	*274*	*208*	*164*	*139*	*123*	*92*	*93*	*101*

* Technically unsatisfactory samples.

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the controls is the positive finding emerging from this study. Its mechanism is unknown.

Summary. Intravenous glucose tolerance tests were performed on 11 peptic ulcer patients and 9 normal controls before and after the administration of an adrenergic blocking agent, Regitine, in an attempt to evaluate the role of adrenalin and stress in a previously described abnormality in the carbohydrate metabolism of ulcer patients. No confirmation of this abnormality could be obtained, the glucose tolerance tests in the ulcer patients being not significantly different from those of the normal controls. Both controls and patients showed a slight hyperglycemia after Regitine. The theories of hormonal influences in ulcer patients and carbohydrate metabolism are discussed.

ACKNOWLEDGMENT: The authors wish to express their appreciation to members of the staff and interns of Mercer Hospital, who furnished patients and controls for this study, and particularly to Mr. Thomas Egan, B.S., M.T. (A.S.C.P.), who performed the glucose determinations.

REFERENCES

1. **Bearn, A. G., Billing, B. H.,** and **Sherlock, S.:** Clin. Sci., **11,** 151, 1952.
2. **Best, C. H.,** and **Taylor, N. B.:** The Physiological Basis of Medical Practice. Baltimore: Williams & Wilkins Company, 1950, p. 676.
3. **Burns, T. W., Engel, F. L., Viau, A., Scott, J. L., Jr., Hollingsworth, D. R.,** and **Werk, E.:** J. Clin. Invest., **32,** 781, 1953.
4. **Cavellero, C.,** and **Malandra, B.:** Acta endocrinol., **13,** 79, 1953.
5. **Cushing, H.:** Surg., Gynec. and Obst., **55,** 1, 1932.
6. **deDuve, C.:** Lancet, **2,** 99, 1953.
7. **Ellis, S., Anderson, H. L., Jr.,** and **Collins, M. C.:** Proc. Soc. Exper. Biol. & Med., **84,** 383, 1953.
8. **Engel, F. L.:** Endocrinology, **45,** 170, 1949.
9. **Folin, O.,** and **Wu, H.:** J. Biol. Chem., **41,** 367, 1920.
10. **Gray, S. J., Ramsey, C., Reifenstein, R. W.,** and **Benson, J. A.:** Gastroenterology, **25,** 156, 1953.
11. **Hecht, H. H., Crandall, R.,** and **Samuels, L. T.:** Fed. Proc., **9,** 283, 1950.
12. **Kibler, R. F.,** and **Myers, J. D.:** Am. J. Med., **14,** 753, 1953.
13. **Laurence, D. R.,** and **Stacey, R. S.:** Brit. J. Pharmacol., **7,** 255, 1952.
14. **Lenoir, P., DeFossey, M.,** and **Richet, C.:** Arch. des Mal. de L'App. Digestif., **11,** 393, 1921.
15. **Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L.,** and **Barrett, T. F.:** Am. J. Med., **14,** 265, 1953.
16. **Meyer, R. J.:** J. Clin. Endocrin. and Metab., **13,** 123, 1953.
17. **Miller, M., Craig, J. W.,** and **Woodward, H., Jr.:** J. Clin. Invest., **32,** 591, 1953.
18. **Mirsky, I. A., Block, S., Osher, S.,** and **Broh-Kahn, R. H.:** Ibid., **27,** 818, 1948.
19. **Platt, W. D., Dotti, L. B.,** and **Beekman, R. S.:** Gastroenterology, **13,** 20, 1949.
20. **Sandweiss, D. J.,** Ed.: Peptic Ulcer: Clinical Aspects, Diagnosis and Management. Philadelphia: W. B. Saunders Company, 1952.
21. **Schechter, S. E.,** and **Necheles, H.:** Gastroenterology, **12,** 258, 1949.
22. **Shay, H.** and **Sun, D. C. H.:** Am. J. Med. Sci., **228,** 630, 1954.
23. **Sterling, R. E.,** and **Longwell, B. B.:** Endocrinology, **53,** 98, 1953.
24. **Strand, F. L.,** and **Gordon, A. S.:** Ibid., **53,** 37, 1953.
25. **Trapold, J. H., Warren, M. R.,** and **Woodbury, R. A.:** J. Pharmacol. & Exp. Therap., **98,** 32, 1950.

ESTERASE AND LIPASE ACTIVITY OF LEUKOCYTES AND ERYTHROCYTES IN HEALTH AND DISEASE*

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Previous studies on the lipolytic activity of human and animal tissues have shown considerable variation in different species and tissues both in regard to substrates hydrolyzed and in regard to the effects of disease. The term aliesterase[12] is used to denote those esterases which hydrolyze esters composed of short chain fatty acids, except cholinesterase, while the term lipase is ordinarily reserved for enzymes hydrolyzing esters of long chain fatty acids. This terminology is employed in both instances irrespective of the alcohol component of the ester.

Esterase activity has been demonstrated in both leukocytes[1,18] and erythrocytes[1] and lipase[1] activity in leukocytes. Grogg and Pearse[9] by histochemical method studied esterase as well as acid and alkaline phosphatase in experimental tuberculosis. In mice, they found esterase in some of the mononuclear phagocytes of the pulmonary tubercles, but esterase activity in these lesions was less than normal lung, in which septal cells showed considerable esterase activity. The monocytes of the peripheral blood, as well as the neutrophils, occasionally had a weakly positive test for esterase. In rats, esterase activity could not be demonstrated in the tuberculous lesion; however, the monocytes of the peripheral blood in some experimental as well as control animals showed fairly strong esterase activity and the neutrophils a very weak reaction. The giant cells of tuberculous lesions of some guinea pigs showed esterase activity, as did the necrotic centers of the lesions and the polymorphonuclear leukocytes. In rabbits, mononuclear phagocytes within the lesions gave a strong reaction for esterase, as did the peripheral monocytes, although this was not demonstrated in the necrotic material or in the neutrophils.

Esterase activity has also been demonstrated in normal rabbit marrow

*This investigation was supported by research grant Number H–1069 (C3R) from the National Cancer Institute of the National Institutes of Health, Public Health Service, and by a grant from Parke, Davis & Company, Detroit, Mich.

together with acetoacetate utilization and production[7] indicating the presence of enzymatic machinery for metabolizing fats. It has also been noted that rabbit marrow is as active in this respect as rat liver, kidney, or lung, and more active than rat heart, skeletal muscle, or pancreas.

In a clinical study[5] of liver catalase and esterase activity made on material obtained by punch biopsy, a decrease in these enzymes was noted in human subjects with infectious hepatitis, but only a slight inconstant decrease was found in nutritional hepatitis associated with alcoholism. It has been suggested that the decrease of these constituents in liver tissue in infectious hepatitis may be due either to the effect on cell enzyme systems of toxic material formed by the action of virus on liver cells, or to interference with the metabolic processes necessary for formation of new enzyme material. Rats placed on an 8% casein diet showed a 45% reduction in liver esterase activity within 2 weeks and, if placed on a protein free diet, a 70% reduction was observed within a week[13]. Normal values could be restored within 2 to 3 weeks on a 21% casein diet. This suggests a possible cause for the decrease occasionally seen in nutritional hepatitis. A marked decrease in liver esterase was also noted with therapeutic doses of Antabuse, and this promptly returned to normal after discontinuance of the drug[5].

Smith *et al.*[21], in 1949, studied the effect of chloramphenicol on various enzyme systems of *E. coli* and other bacteria and found only esterase inhibition among 45 enzyme systems studied. The antibiotic did not inhibit cellular respiration of either actively growing or resting bacteria. Phosphorylative carbohydrate metabolism was not blocked, and the breakdown of protein into amino acids and their transamination was not affected. At low concentrations of chloramphenicol (0.8 to 1.0 micrograms per cc.) there was no significant change in esterase activity, but with concentrations of 1 to 3 mcg. there was definite inhibition of enzymatic activity which in some cases decreased as much as 25%. Concentrations of 3 to 50 mcg. per cc. produced marked stimulation of enzyme activity with as much as 50 to 80% increase, but when the concentration of the antibiotic exceeded 50 mcg. per cc. there was almost complete inactivation of bacterial growth and esterase activity. The anti-esterase effect on mitochondria and animal cell homogenates was quite different. Here the drug inhibited only 40 to 50% of the esterase activity, and at high concentrations of 100 mcg. per cc. there was no inhibition. In a recrystallized preparation of horse liver esterase, however, the same inhibition was found as observed in bacterial systems. Hence in the animal there is apparently a barrier at the cell or at the mitochondrial surface, or both, which prevents the action of chloramphenicol on the cell esterase.

Since chloramphenicol may in certain individuals have toxic effects on the hemopoietic system[11,22], and since lipolytic activity has been noted for both leukocytes and erythrocytes as well as bone marrow, an investigation of leukocyte and erythrocyte esterase and lipase was undertaken to determine normal levels of activity in man, variations if any in leukocyte populations of different morphological types, the effect of disease on these activities, and the effect of chloramphenicol *in vitro*.

Material and Methods. REAGENTS. 1. *Beta Naphthol acetate* was used as a substrate for esterase activity, and was prepared according to the description of Nachlas and Seligman[14]. Five hundred milligrams of the reagent were dissolved in 100 cc. of acetone and used as a stock solution which was stored in the re-

frigerator without hydrolysis. To prepare the substrate, 2.0 cc. of the stock Beta Naphthol acetate was added to 70.0 cc. of tris buffer (tris hydroxymethyl aminomethane) and 8.0 cc. of water. This was prepared immediately before use, as marked non-enzymatic hydrolysis occurred over a 24-hour period on storage.

2. *Beta Naphthol laurate* was used as a substrate for lipase activity and was prepared as described by Nachlas and Seligman[15]. Fifty milligrams of Beta Naphthol laurate were dissolved in 25 cc. of acetone, and this was stored in the refrigerator as a stock solution. The substrate was then prepared by adding 1.0 cc. of the stock solution with a submerged pipette while swirling into 19.0 cc. of tris buffer immediately before use. The buffered solution could not be stored because of marked non-enzymatic hydrolysis over a 24-hour period.

3. *Tris hydroxymethyl aminomethane*[8] as obtained from Commercial Solvents Co. was used as a buffer at pH 7.4 in 0.05M concentration.

4. Sodium taurocholate solution in concentration of 8×10^{-2}M. (890 mg. per 100 cc.), as obtained from Dajac Laboratories of Leominster, Mass., was used as an esterase inhibitor[15,20] in the lipase experiments.

5. *Naphthanil Diazo Blue B* (*Tetrazotized diorthoanisidine*) was prepared immediately before use by dissolving 80 mg. in 20 cc. of cold water. (Obtained from Dajac Labs.)

6. *Forty per cent Trichloracetic acid.*

7. *Ethyl acetate.*

METHODS. A modification of the method described by Nachlas and Seligman[15] for serum esterase and lipase activity was used. The separation of leukocytes and erythrocytes was accomplished by use of Armour's Bovine Fibrinogen (Fraction I) as an erythrocyte sedimenting agent[4,23]. In addition to Fraction I, phythemaglutinin* was added to effect a more complete separation of the leukocytes from erythrocytes. The erythrocyte and leukocyte suspensions were prepared as described previously[10], and were then washed twice with saline to remove any serum esterase or lipase contamination. After washing the cells, they were suspended in appropriate quantities of saline and triplicate red and white cell counts done on each suspension. In the erythrocyte rich suspension, leukocyte counts were done only in duplicate since leukocyte contamination was largely negligible.

Effective release of enzyme from cells was achieved by the addition of 2 volumes glass distilled water to cell suspensions. An aqueous suspension or homogenization[3] of either a saline or aqueous suspension all failed to give superior results. The use of saponin was unsatisfactory because of color reactions with the dye reagent.

As a result of the rather marked esterase activity of both leukocytes and erythrocytes when the incubation was carried out for 20 minutes at 37° C., it was found advantageous to perform the incubation in the cold room in a water bath at 4° C. The reaction rate for erythrocytes was found to be linear over a 60-minute period and for leukocytes over a 45-minute period. Consequently the procedure for both erythrocytes and leukocytes was done at 4° and for a 45-minute incubation period.

The method for esterase determination as described by Nachlas and Seligman[15] was modified slightly in that tris hydroxymethyl aminomethane replaced the barbiturate buffer. For the incubation, 1.0 cc. of the cell suspension was pipetted into an NPN tube and 2.0 cc. of glass distilled water added to lyse the cells. After 5 minutes equilibration, 4 cc. of substrate was added and the incubation carried out for 45 minutes. At the end of this time, 1.0 cc. of freshly prepared solution of "dye" (Naphthanil Diazo Blue B) was added and 3 minutes later 1.0 cc. of 40% trichloracetic acid was employed to stop the reaction and facilitate extraction of azo dye. The color was immediately extracted with 15 cc. of ethyl acetate. To measure the non-enzymatic hydrolysis of the substrate, blanks were prepared in which addition of the cell suspension was made at the end of the incubation after the reaction had been stopped with trichloracetic acid.

Lipase activity was determined by using Beta Naphthol laurate as a substrate in the presence of sodium taurocholate[15,16,19]. A 5-hour incubation period at 37° C. was necessary in order to measure appreciable lipase activity. For the incubation, 1.0 cc. of sodium taurocholate was added to 1.0 cc. of the leukocyte suspension followed by 5.0 cc. of the substrate. After the incubation period, color development and extraction of the dye were accomplished in the same manner as described for esterase activity. A blank was prepared as in the esterase reaction. The color intensity of unknowns was measured in a Model B Beckman spectrophotometer at

*Generously supplied by Dr. Demitrios Rigas, University of Oregon School of Medicine, Portland, Oregon.

540 mμ. (Absorption spectra showed that the maximal light absorption was at 540 mμ.) A standard curve was determined with β Naphthol and was found to follow Beer's Law in concentrations from 8 to 56 mcg. per cuvette. Esterase and lipase activity were interpreted directly from the standard curve on the basis of duplicate determinations for both erythrocytes and leukocytes. Duplicate determinations rarely showed more than 10% error, and any determination of 16% or greater discrepancy was discarded. Values are expressed in terms of milligrams of Beta Naphthol liberated per hour from substrate by 10^{10} cells at 4° C. in the case of esterase and at 37° C. in the case of lipase. The presence of a significant contribution to esterase activity by contaminating erythrocytes in the leukocyte rich suspensions required correction of leukocyte esterase values for this contamination. The leukocyte contamination of erythrocyte rich suspensions was usually negligible. Lipase activity could be calculated directly.

Recovery of added Beta Naphthol ranged from 96.5 to 103% when aliquots of standard Beta Naphthol were added to unknown flasks at the beginning of the incubation period.

Results. NORMAL SUBJECTS. Twenty-two determinations were done on 20 healthy individuals of varying ages. These patients were in apparent good health and were selected from the surgical wards prior to elective surgery for hernia, varicose veins, and the like, which would not preclude normalcy. The erythrocyte esterase in this group expressed as indicated above ranged from 1.7 to 4.8 mg. with a mean of 3.2 mg., while the leukocyte values varied from 10.1 to 27.6 mg. with a mean of 16.3. The data indicate a fairly narrow range of erythrocyte esterase, a rather marked spread of leukocyte esterase, and a mean leukocyte/erythrocyte ratio of 5 to 1. However, the latter varied considerably with individual cases.

Leukocyte lipase activity showed a fairly narrow range of 0.7 to 3.2 mg. with a mean of 1.6 mg. A direct comparison of leukocyte esterase and lipase activity should not be made in any of the patient categories since the esterase incubation was done at 4° C. and the lipase at 37°, though all are based on calculations for a one-hour period. No lipase activity was demonstrable in any of the erythrocyte preparations. Esterase and lipase activity of leukocytes and esterase activity of erythrocytes in these normal subjects and in subjects with various disease states subsequently reported are shown in a scattergram in Fig. 1.

ESTERASE ACTIVITY OF GRANULOCYTIC LEUKOCYTES IN DISEASE. Various disease states characterized by predominantly granulocytic leukocyte populations were studied, including specific infections, neutrophilia of non-infectious origin, polycythemia vera, myeloproliferative syndromes[6] of unknown etiology and granulocytic leukemia. The leukocyte esterase activity in these disease categories showed a rather marked variation, the mean value being 13.7 mg. as compared to 16.3 mg. for normal controls. The lowest value of 5.0 mg. was obtained in a man with metastatic carcinoma of the stomach following a palliative gastric resection because of severe gastric bleeding. One week after the first determination, there was considerable temporary clinical improvement and the esterase had increased to 9.7 mg., a value only slightly below the lower limit found in normal adults. A low value of 8.4 mg. was also noted in one instance in the infectious group, and this increased 3 weeks later to 15.7 mg. after the infection had cleared.

The range of esterase values was essentially normal in 8 patients with polycythemia rubra vera who showed a neutrophilia or myeloid immaturity, or both, with a mean of 15.1 mg., but 2 subjects showed low values of 8.4 and 9.7 mg. respectively. In both of these patients the peripheral blood showed marked immaturity of the granulocytic leukocytes with many blast

forms and early myeloid cells present.

Four determinations were done on 3 patients with myeloproliferative syndromes[6] thought to be neither polycythemia vera nor granulocytic leukemia. These syndromes were of unknown etiology and characterized by an abnormal proliferation of blood-forming tissue, granulocyte immaturity, anemia, splenomegaly, and hepatomegaly. Leukocytosis had been demonstrated previously in all of these patients, but was not present at the time of these studies. A low value of 5.2 mg. was observed in one patient while the other determinations were within the normal range.

Five patients with chronic granulocytic leukemia were studied on 16 occasions. A mean of 14.0 mg. and a range of 7.0 to 24.0 mg. was observed. Two of the patients were followed through a course of Roentgen therapy with weekly esterase determinations. In both patients decreased values were noted originally, and these tended to increase during therapy. One patient achieved a normal esterase value at the completion of therapy. In the second subject, after an initial rise, esterase values again started to fall even while therapy was continuing, and 4 weeks after completion of the prescribed irradiation, the esterase activity had returned to its original level. Both patients showed an excellent clinical remission lasting several months, so it was not possible to correlate the clinical course with leukocyte esterase levels. In addition one patient with

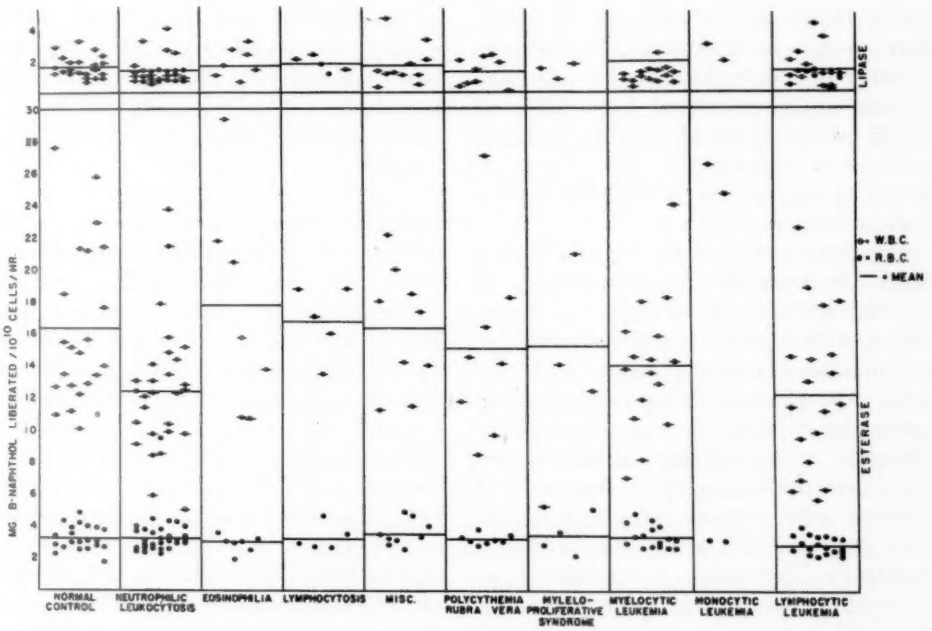

Fig. 1.—Scattergram showing leukocyte and erythrocyte esterase activity and leukocyte lipase activity in normal subjects and subjects with disease. Esterase activity is expressed as milligrams of Beta Naphthol liberated per hour from substrate Beta Naphthol acetate *at 4° C.* by 10^{10} leukocytes or erythrocytes. Lipase activity is expressed as milligrams of Beta Naphthol liberated per hour from substrate Beta Naphthol laurate *at 37° C.* by 10^{10} leukocytes. No lipase activity was demonstrated in erythrocytes.

chronic granulocytic leukemia and a very high percentage of circulating basophils ranging up to 67% was studied on several occasions. Leukocyte esterase was at all times within the normal range. At a time when a considerable number of blast forms were also present the activity was greatest but still normal.

Six subjects with eosinophilia who were studied on 7 occasions showed a mean leukocyte esterase of 17.6 mg. and a range of 10.8 to 29.33. The percentage of eosinophils in the cell population analyzed varied from 15.5% to 57.5%, and the patient with the greatest number of eosinophils showed a value of 15.8 mg. which is essentially the normal mean.

ESTERASE ACTIVITY IN DISEASE STATES CHARACTERIZED BY LYMPHOCYTOSES. In 5 determinations performed on 4 patients with benign lymphocytosis due to infectious mononucleosis and one with unexplained lymphocytosis following an iridectomy, all values were found to be essentially normal. Seventeen determinations were done on 11 patients with chronic lymphocytic and on 2 patients with acute lymphoblastic leukemia. The range in chronic lymphocytic leukemia was from 5.6 to 22.5 mg. with a mean of 12.3 mg. per 10^{10} leukocytes. The two subjects with acute lymphoblastic leukemia showed values near the normal mean. The patient with chronic lymphocytic leukemia showing the lowest value was followed through a course of Roentgen therapy. While receiving therapy, esterase values increased to normal. Follow-up studies could not be completed due to the development of a marked leukopenia. There was no particular correlation of esterase activity with cell maturity or total leukocyte count. Some patients in this group with a marked increase in total count showed normal values, while others with counts only slightly elevated had low leukocyte esterase activity.

ESTERASE ACTIVITY IN MISCELLANEOUS DISEASE STATES. Two patients with monocytic leukemia were studied. In both subjects, leukocyte esterase and lipase values were at the upper limits of the normal range. Also studied were patients with Laennec's cirrhosis, sickle cell disease, paroxysmal nocturnal hemoglobinuria, pancreatitis, lupus erythematosus, and one patient convalescing from a cerebrovascular accident who had received ACTH gel for a 72-hour period. In all cases erythrocyte and leukocyte esterase values were normal.

EFFECT OF CHLORAMPHENICOL ON ESTERASE ACTIVITY IN VITRO. In a study of the effect of chloramphenicol *in vitro*, 22 determinations were performed. Most determinations were made on patients with neutrophilic leukocytosis, but one patient each with chronic lymphocytic leukemia, polycythemia rubra vera, and myeloproliferative syndrome was also included. Several methods were used for determination of possible inhibition. Initially, incubation of a cell suspension was carried out at 37° C. with concentrations of chloramphenicol of 4.6, 233, and 500 mcg. per cc. After incubation with chloramphenicol the suspension was allowed to equilibrate in the 4° water bath, substrate was added, and esterase assay determined in the usual manner. Because of loss of esterase activity in control determinations done in this manner, it was decided to incubate the cells with chloramphenicol in concentrations of 100 to 2500 mcg. per cc. in the cold water bath (4°) for 2 hours before addition of the substrate. In a portion of the incubations, the cells were homogenized with the antibiotic. In others it was added after homogenization, and in the remaining cases homogenization was not carried

out. The inhibition due to the drug was not at all impressive. In 2 instances there was slightly greater hydrolysis than in the controls, but this was not considered significant. In 6 instances there was no inhibition; and in only 5 determinations was there inhibition of 15% or greater (15, 16, 19, and 31%). Inhibition by chloramphenicol when it occurred did not seem to bear any definite relationship to concentration, method of incubation, or preparation of cells, that is, homogenization did not effect the inhibition. Almost all of the chloramphenicol inhibitions were paired studies, using the same patient for 2 concentrations of the drug. When inhibition was noted, it always increased with an increasing concentration of the antibiotic. However, the same concentration of chloramphenicol did not produce the same degree of inhibition in each patient studied. For example, a concentration of 500 mcg. per cc. in one patient gave 31% inhibition, and in another no inhibition.

Discussion. A quantitative comparison of the foregoing data with previous observations in other tissue cannot be made because of differences in methodology and mode of expression of data. Nachlas and Seligman[14] have reported esterase activity in human liver equivalent to the liberation of 1 to 2 micromoles of Beta Naphthol per mg. of liver *dry weight* per hour. Assuming 10^{10} leukocytes have a wet weight of roughly 4.0 gm.[17] our data would give values of 0.028 micromoles of Beta Naphthol hydrolysed per hour per mg. *wet weight* of leukocytes. Since esterase activity in these studies was for convenience measured at the low temperature of 4° C., it is apparent that very substantial esterase activity is present in human leukocytes. A comparison of the above data with that of Rossiter and Wong[18] on rabbit leukocytes is rendered difficult because of differences in the methods employed. In these studies, lipase activity was found only in leukocytes, while both leukocytes and erythrocytes possessed appreciable esterase activity with an average ratio of 5:1. Erythrocyte esterase did not show any significant variation in any of the disease states studied. With the possible exception of monocytic leukemia, the leukocyte lipase activity did not show any significant variation from the average mean. The data on erythrocyte esterase and leukocyte lipase activities in disease has, therefore, not been presented in detail but is documented on the scattergram in Fig. 1.

The data obtained, while not permitting exact quantitative correlation, give strong inferential evidence as to the distribution of esterase and lipase activity among the various morphological leukocyte types. Esterase activity was normal on a per cell basis in cases of infectious mononucleosis in which high percentages of lymphocytes were present. Although in many subjects with chronic lymphocytic leukemia esterase activity was in the normal range, in some, low values were observed. There was no apparent explanation for decreased values in those subjects in which these were found and no correlation with clinical status. In chronic lymphocytic leukemia, the unit cell nitrogen content has been found to be approximately a little less than half that in normal blood containing leukocytes in normal proportions[2]. Expressed in terms of cell nitrogen instead of cell numbers, therefore, lymphocyte esterase activity in the majority of instances was substantially greater than that observed where the predominating cell was the polymorphonuclear leukocyte. It is of interest that predominantly lymphoblastic cell population in acute lymphoblastic

leukemia also yielded normal esterase values.

No subjects were studied in which the non-leukemic monocyte was the predominating cell. However, in 2 subjects with monocytic leukemia marked esterase activity was observed, suggesting that the leukemic monocyte and perhaps the normal monocyte possess very substantial esterase activity.

Most patients with neutrophilia showed normal esterase values indicating that the polymorphonuclear leukocyte shares in the ubiquitous distribution of this enzyme. Values were low in one subject with acute epididymitis and one subject showed a very low value following a palliative gastric resection for carcinoma. In the former instance the cause for the low value which returned to normal after recovery is not clear though "toxic" inhibition of esterase has been postulated under other circumstances. In the latter instance, esterase values increased with improved nutritional status, and the very low value initially observed might be related to low protein intake as demonstrated for liver esterase in experimental animals. In chronic granulocytic leukemia, where cell populations were less mature but predominantly granulocytes at the myelocyte stage of development or beyond, esterase values were normal or very moderately depressed. Rather marked esterase and lipase activity was noted in the patient in the series in whom most granulocytic immaturity was present. In subjects with high grade eosinophilia these enzymatic constituents were normal or elevated, and in a single subject in whom basophils constituted as high as 67% of the leukocytes, values were also repeatedly in the normal range. The evidence indicates that esterase activity is probably diffusely distributed throughout the leukocytes of all morphological types of both mononuclear and granulocytic series, and that it is present even in the most immature members.

Summary. A brief review of the lipolytic activity of certain human and animal tissue is presented. Esterase activity was determined for erythrocytes and leukocytes by means of an azo dye using the chromogenic substrate Beta Naphthol acetate. Lipase activity was determined for leukocytes by use of the same method with Beta Naphthol laurate as a substrate in the presence of Sodium taurocholate as an esterase inhibitor; lipase activity in erythrocytes was not demonstrated. The data demonstrated: 1) A narrow range for erythrocyte esterase and leukocyte lipase without significant variation between normal controls and patients with various disease states. Leukocyte esterase showed considerable variation with a rather large spread in the control series. 2) A leukocyte erythrocyte esterase ratio of approximately 5 to 1. 3) Esterase activity of leukocytes greatly exceeded lipase activity. 4) Lymphocytes from patients exhibiting benign lymphocytosis demonstrated esterase activity comparable to that of the leukocytes of normal blood on a per cell basis but actually somewhat greater than normal when expressed on the basis of cell nitrogen. 5) In 6 subjects with high percentages of eosinophils and one subject with a markedly elevated basophil percentage normal values were found suggesting that esterase activity is present in both eosinophils and basophils. 6) Patients with neutrophilia who demonstrated decreased esterase activity approached or reached normal levels with clinical improvement. 7) Patients with myelocytic leukemia showed a mean leukocyte esterase below that of the controls, but within the normal range. 8) The effect of chloramphenicol on leukocyte esterase was studied.

ACKNOWLEDGMENTS: The authors gratefully acknowledge technical assistance of Mrs. Gertrude Duncan, Mr. Peter Shugarman, and Miss Elinor Siegel in performing the determinations of enzymatic activity.

REFERENCES

1. **Ammon, R.,** and **Jaarma, M.:** In **Sumner, J. B.,** and **Myrback, K.,** The Enzymes. New York: Academic Press, **1,** pp. 390–472, 1950.
2. **Beck, W. S.:** Personal communication, 1953.
3. **Brendler, H.:** Science, **114,** 61, 1951.
4. **Buckley, E. S., Jr., Powell, M. J.,** and **Gibson, J. G., II:** J. Lab. & Clin. Med., **36,** 29, 1950.
5. **Dale, B. G.:** Am. J. Med. Sci., **226,** 42, 1953.
6. **Dameshek, W.:** Blood, **6,** 372, 1951.
7. **Evans, J. D.:** Am. J. Physiol., **171,** 48, 1952.
8. **Gomori, G.:** Proc. Soc. Exper. Biol. & Med., **62,** 33, 1946.
9. **Grogg, E.,** and **Pearse, A. G. E.:** Brit. J. Exper. Path., **33,** 567, 1952.
10. **Hardin, B., Valentine, W. N., Follette, J. H.,** and **Lawrence, J. S.:** Am. J. Med. Sci., **228,** 73, 1954.
11. **Hodgkinson, R.:** Lancet, **1,** 285, 1954.
12. **Huggins, C.,** and **Lapides, J.:** J. Biol. Chem., **170,** 467, 1947.
13. **Meikleham, V., Wells, I. C., Richert, D. A.,** and **Westerfeld, W. W.:** Ibid., **192,** 651, 1951.
14. **Nachlas, M. M.,** and **Seligman, A. M.:** J. National Cancer Inst., **9,** 415, 1949.
15. Iidem: J. Biol. Chem., **181,** 343, 1949.
16. **Ravin, H. A.,** and **Seligman, A. M.:** Arch. Biochem. and Biophys., **42,** 337, 1953.
17. **Rossiter, R. J.,** and **Wong, E.:** Canad. J. Research, **28,** 69, 1950.
18. Iidem: J. Biol. Chem., **180,** 933, 1949.
19. **Seligman, A. M.:** Personal communication, 1953.
20. **Seligman, A. M.,** and **Nachlas, M. M.:** J. Clin. Invest., **29,** 31, 1950.
21. **Smith, G. N., Worrel, C. S.,** and **Swanson, A. L.:** J. Bact., **58,** 803, 1949.
22. **Thompson, H. E.,** and **Rowe, H. J.:** Ann. Int. Med., **39,** 1124, 1953.
23. **Valentine, W. N.,** and **Beck, W. S.:** J. Lab. & Clin. Med., **38,** 39, 1951.

ACQUIRED AGAMMAGLOBULINEMIA WITH HYPERSPLENISM* A CASE REPORT

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Bruton[3], in 1952, first reported the case of a child with agammaglobulinemia who demonstrated no immune response against a variety of bacterial infections. He was of the opinion that the child's inability to form gamma globulin was an hereditary defect. Following this initial report other investigators[4,6,7] found additional cases showing similar laboratory and clinical features. This clinical syndrome was first recognized in an adult by Zinneman[15] in 1953. Additional cases of agammaglobulinemia in adults were reported by Sanford *et al.*[11], Young and Wolfson[14], Good[5], Saslaw and Wall[12], and Zinneman *et al.*[16].

The criteria for acceptance of the clinical syndrome of agammaglobulinemia would seem to require the following findings: (1) a history of repeated bacterial infections, (2) absence of naturally occurring antibodies and acquired antibodies against bacteria with normal viral antibody mechanisms, (3) gamma globulin levels of less than 30 micrograms per cent, (4) protection against bacterial infections by maintenance injections of gamma globulin.

An interesting complication of this syndrome was reported by Prasad and Koza[9] who found an acquired hemolytic anemia responding promptly to splenectomy in an adult female with agammaglobulinemia.

Confirmation of this finding and a report of additional hypersplenic mechanisms is illustrated in the following case.

Case Report. The patient was a 29-year-old white male who was admitted to the medical service of the Indiana University Medical Center on March 9, 1954, with a 7-month history of progressive weight loss of 53 pounds, weakness, cough, hemoptysis, and occasional cramping periumbilical pains. Prior to admission he had received a course of streptomycin and PAS therapy because tuberculosis had been suspected although this diagnosis had never been established. Past history revealed that patient had been in good health until 1944 when he was hospitalized because of diarrhea and weight loss of 3-months' duration. At this time a diagnosis of a sprue-like syndrome was made; treatment consisted of diet and supplementary vitamins. Unfortunately no serum protein determinations were made at this time. Throughout the following years he was subject to repeated episodes of diarrhea. Physical examination at the time of the present admission revealed

*Presented at the Twelfth Annual Meeting of the Midwestern Section of the American Federation for Clinical Research, October 28, 1954, Chicago, Illinois.

TABLE 1.—LABORATORY DATA

Hematological studies (on admission to hospital)	
Hemoglobin	5.1 gm.
Red blood count	2.51 million/c.mm.
White blood count	1400/c.mm.
Neutrophils	78%
Basophils	2%
Lymphocytes	12%
Monocytes	8%
Platelet count	182,400/c.mm.
Reticulocyte count	9.7%
Erythrocyte sed. rate	30 mm./hr.
Hematocrit	33%
Bone marrow	Granulocytic and erythroid hyperplasia. Marked reduction of lymphocytes and plasma cells
Urinalyses	Intermittently loaded with pus cells
B.M.R.	+5.9%
Electrocardiogram	Normal
Stool examinations	No ova or parasites found
Blood Chemistry determinations	
Fasting blood sugar	76 mg. per 100 cc.
Nonprotein Nitrogen	32 mg. per 100 cc.
Serum Sodium	139 mEq./L.
Serum Potassium	4.3 mEq./L.
Serum Chloride	93 mEq./L.
Plasma CO_2	27.8 mEq./L.
Alkaline Phosphatase	4.3 King and Armstrong units
Total serum bilirubin	0.6 mg. per 100 cc.
indirect	0.4 mg. per 100 cc.
direct	0.2 mg. per 100 cc.
Prothrombin time	15.6 seconds (82%)
Congo red test	2% of dye eliminated from serum in one hour
Total serum protein	4.4 gm.%
Albumin	4.03 gm.%
Globulin	0.37 gm.%
Bacteriological studies	
Urine cultures	*E. freundii, M. pyogenes* var. *aureus,* Beta hemolytic streptococci
Stool culture	*M. pyogenes* var. *aureus*
Sputum culture, Gastric washings, Bone marrow culture	All were negative for acid-fast bacilli and fungi
Immunological studies	
Agglutination tests	
S. typhosa O and *H*	Negative
B. abortus	Negative
Cold Agglutinins	Negative
Patient's serum plus trypsinized cells	No agglutination
Patient's cells plus developing serum	No agglutination
Complement fixation tests	
Blastomyces dermatiditis	Negative
Coccidioides immitis	Negative
Histoplasma capsulatum	Negative
Serological test for syphilis	Negative
Skin Tests	
Tuberculin test (2nd strength P.P.D.)	Negative
Schick test	Pseudoreaction
Coccidioidin	Negative
Blastomycin	Negative
Histoplasmin	Negative

a cachectic pale, white male who appeared chronically ill. Temperature was 100° F. Teeth were carious with pyorrhea alveolaris. Blood pressure was 104/70. Heart rate was 96 per minute and regular. There was a soft apical systolic murmur. Heart was not enlarged. Spleen was markedly enlarged extending 2 cm. below the level of the umbilicus. Liver was palpable 2 cm. below the right costal margin. There was a generalized lymphadenopathy with the nodes firm and rubbery in consistency and varying from 0.5 to 2 cm. in diameter. Laboratory data are summarized in Table 1. Electrophoretic curves (Figs. 1 and 5) showed an absence of gamma globulin. An intravenous pyelogram, roentgenographic examination of the esophagus, stomach, duodenum and small intestine were all normal. A chest roentgenogram showed only segmental atelectasis. A barium enema revealed distortion and thickening of the mucosal markings of the cecum and ascending colon. Lymph node biopsy showed obliteration of nodal architecture with replacement by hyalinized scar tissue around the periphery of which there was an increase in reticulum cells and only a scattering of lymphocytes.

Because of the marked hypersplenism as manifested by a persistent severe pancytopenia, a splenectomy was performed on March 31, 1954. During surgery the cecum and ascending colon were carefully examined and no evidence of disease could be found. Following splenectomy there was an excellent hematological response with a prompt rise of red cells, platelets and leukocytes. Anticoagulant therapy was instituted when platelets reached a level above 3 million per c.mm. and was continued for several weeks until platelet levels had returned to normal. Because of the absence of gamma globulin, low grade fever, and recurrent infections the patient was given pooled gamma globulin of the type used in the prophylaxis of poliomyelitis in doses varying from 10 cc. to 30 cc. On this therapy he experienced an increase in strength, disappearance of minor cutaneous infections, and diminution in the degree of fever. The effectiveness of the gamma globulin was seen to disappear clinically in 14 to 21 days.

The patient was discharged from the hospital on July 14, 1954, and was readmitted on August 8, 1954, complaining of marked weakness and diarrhea which was found to be the result of a staphylococcal enterocolitis. This was satisfactorily controlled by intramuscular injections of gamma globulin and oral erythromycin therapy. He was discharged on September 4, 1954. He is presently continuing his improved status according to the last follow-up report from the family physician on January 1, 1955.

Discussion. The following tentative classification of the syndromes of agammaglobulinemia, based on various case reports, is suggested.

(1) Familial Lymphopenic Agammaglobulinemia of Infants[1,2]
(2) Adult Agammaglobulinemia
  (*a*) Familial Lymphopenic[11,14]
  (*b*) Familial Nonlymphopenic[14]
  (*c*) Acquired[9,11]
(3) Hypoproteinemia[5,9,11,16]
  (*a*) Idiopathic[13]
  (*b*) Acquired[8]
(4) Hypogammaglobulinemia Secondary to Lymphomas and Myeloma[1,2,10]

Our patient demonstrated a persistent lymphopenia and the Tiselius electrophoretic curve (Fig. 1) showed no demonstrable gamma globulin. It is then a matter of conjecture as to whether this was an hereditary disorder or an acquired defect in the formation of gamma globulin. Certain features suggest to us that his agammaglobulinemia was most likely the acquired type. It would seem unlikely that he would be free of disease until 19 years of age, as he reported, without significant gamma globulin levels. Study of the lymph nodes obtained by biopsy (Fig. 2) demonstrated massive fibrosis and suggested a burned out inflammatory or granulomatous process which would not be anticipated in an hereditary agammaglobulinemia. Study of the electrophoretic patterns and hemograms of the parents and siblings of this patient showed no deviation from the normal patterns observed in our laboratory.

Some features in this patient seem worthy of additional comment. While study of biopsy tissue and bone mar-

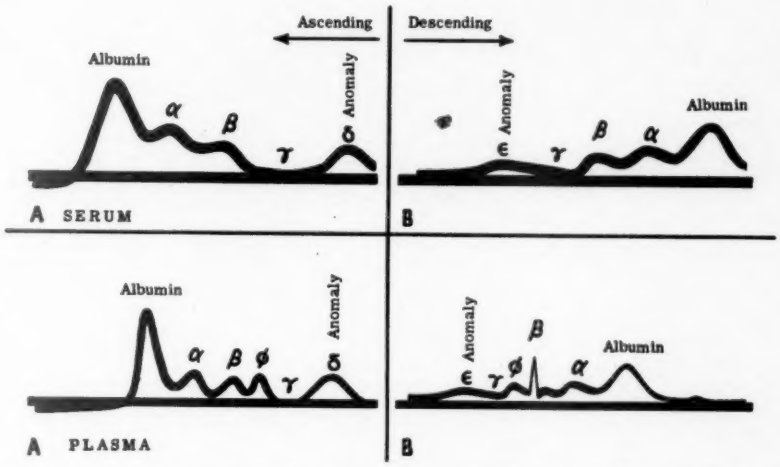

Fig. 1.—Tiselius Electrophoretic Curves Showing Absence of Gamma Globulin in both Serum and Plasma. (These determinations were performed by Dr. E. A. Lawrence and Dr. C. G. Palmer of the Cancer Research Division, Department of Surgery, Indiana University School of Medicine.)

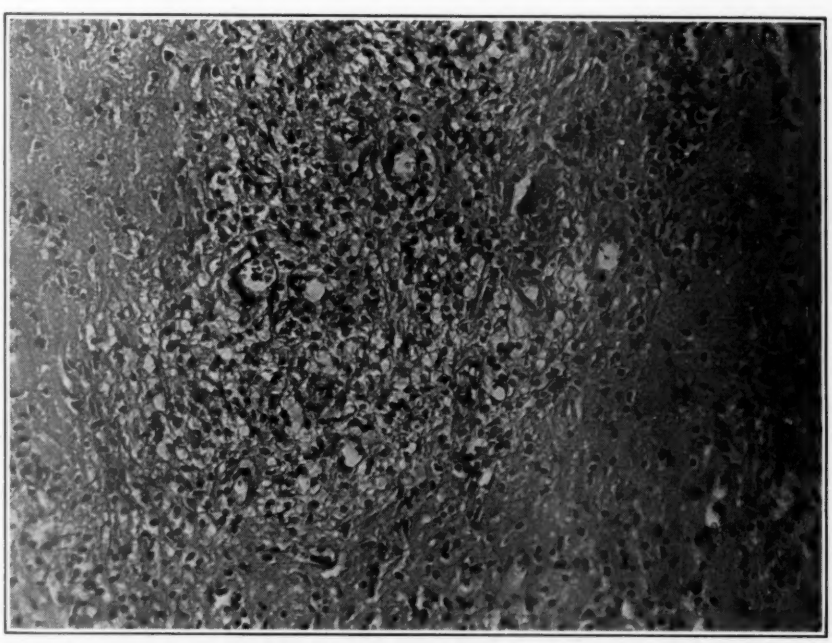

Fig. 2.—Photomicrograph of biopsied lymph node (× 440) illustrating fibrosis and reticulum cell hyperplasia with diminished lymphocytes.

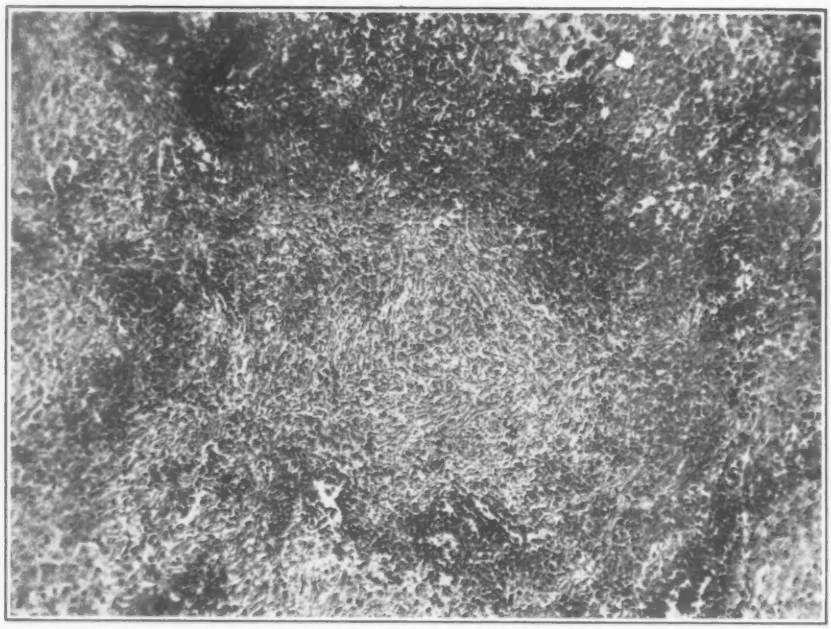

Fig. 3.—Photomicrograph of splenic tissue (× 100) illustrating fibrosis and congestion.

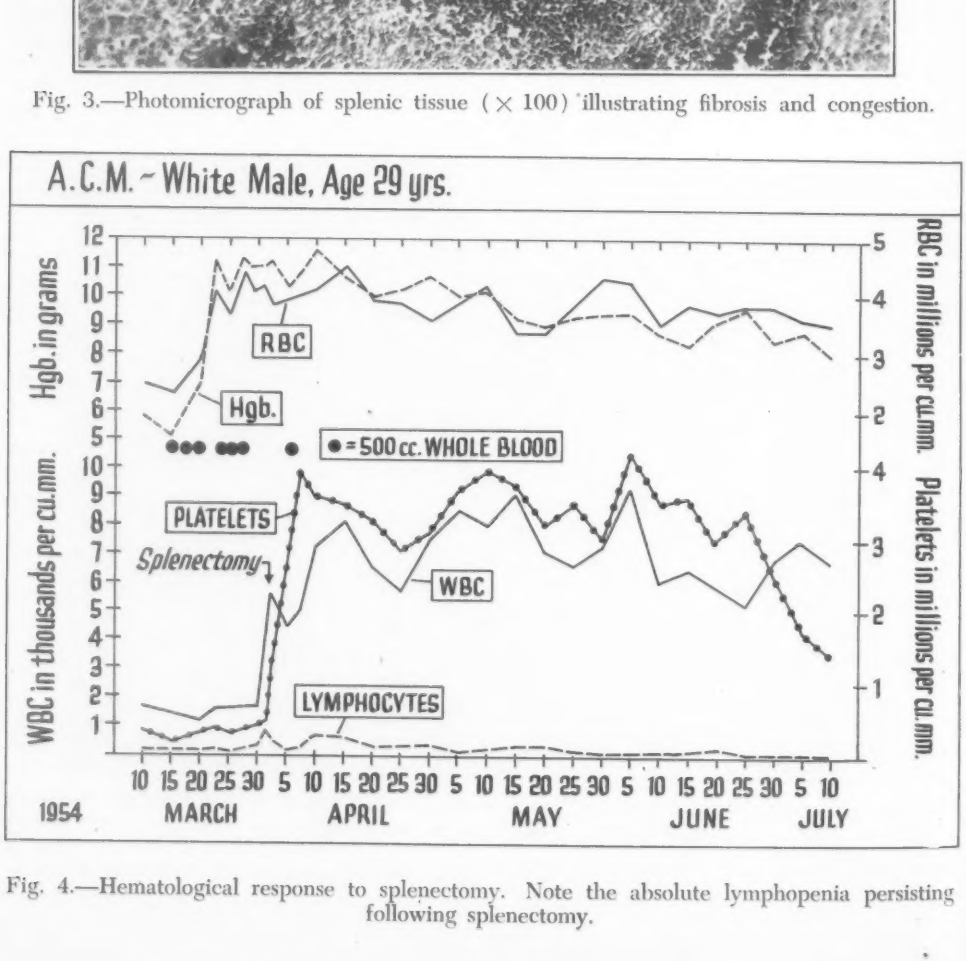

Fig. 4.—Hematological response to splenectomy. Note the absolute lymphopenia persisting following splenectomy.

row aspirate showed a paucity of mature lymphocytes there was almost complete absence of plasma cells in the tissues studied. This is in accord with the findings of Good[5] who has suggested that this cell plays a more important role in the formation of antibodies than does the mature lymphocyte.

increase in highly phagocytic clasmatocytes containing great numbers of phagocytized erythrocytes, platelets, and leukocytes. Certainly in this case, hypersplenism seems to result directly from hyperphagocytosis without intervention of demonstrable humoral antibodies. Response to splenectomy was prompt and excellent (Fig. 4).

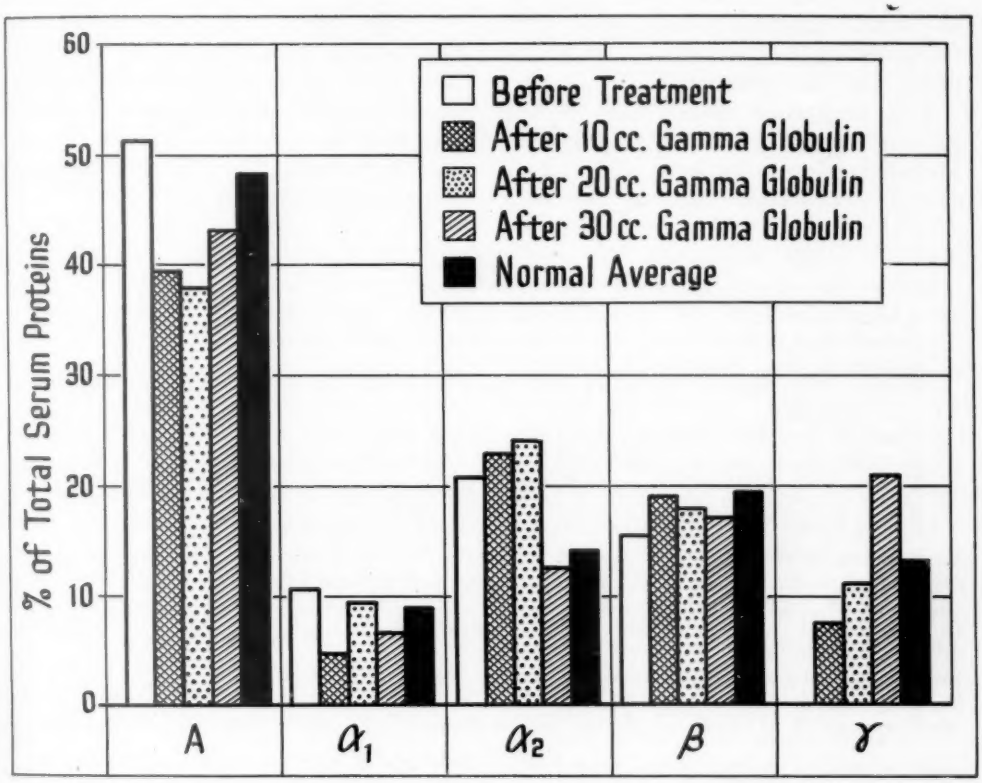

Fig. 5.—Serum protein values as determined by paper electrophoresis, employing barbital buffer pH 8.6, contrasted with normal values observed in this laboratory. Note the complete absence of gamma globulin prior to treatment.

In the absence of antibodies it is suggested that there is compensatory hyperplasia and hyperfunctioning of the phagocytic elements of the reticuloendothelial system in response to infection, and study of splenic tissue, in addition to the demonstrable congestion (Fig. 3), showed marked

This patient was given intramuscular injections of varying quantities of gamma globulin, and the alteration of the gamma globulin curve on paper electrophoresis was plotted in columnar form (Fig. 5). While gamma globulin activity could be demonstrated on paper electrophoresis for 30 or more

days after injection of a single dose of gamma globulin, he began to show clinical deterioration in 14 days to 21 days after such injection. These observations would suggest that the adult with agammaglobulinemia might require an injection of approximately 20 cc. of gamma globulin every 14 to 21 days to be given maximum protection.

Summary and Conclusions. 1. A case of adult agammaglobulinemia with complicating hypersplenic pancytopenia has been presented.

2. A suggested classification of the varying types of the agammaglobulinemic syndrome has been outlined.

3. The available data in the case presented would suggest that this represented an acquired agammaglobulinemia.

4. The hypersplenism would seem to result from the compensatory hyperplasia and hyperfunctioning of the phagocytic elements of the reticuloendothelial system. Removal of the spleen resulted in return to normal of platelet, granulocyte and red cell levels.

5. Alterations in the electrophoretic pattern and their response to injection of varying doses of gamma globulin was illustrated and a suggested intramuscular dosage level of 20 cc. of gamma globulin every 14 days seemed indicated in this patient.

REFERENCES

1. **Adams, W. S., Alling, E. L.,** and **Lawrence, J. S.:** Am. J. Med., **6,** 141, 1949.
2. **Arends, T., Coonrad, E. V.,** and **Rundles, R. W.:** Ibid., **16,** 833, 1954.
3. **Bruton, O. C.:** Pediatrics, **7,** 722, 1952.
4. **Bruton, O. C., Apt, L., Gitlin, D.,** and **Janeway, C. A.:** A.M.A. Am. J. Dis. Child., **84,** 63, 1952.
5. **Good, R. A.:** Proc. Cen. Soc. Clin. Res., **27,** 48, 1954.
6. **Janeway, C. A., Apt, L.,** and **Gitlin, D.:** Tr. Assn. Am. Physicians, **66,** 200, 1953.
7. **Keiden, S. E., McCarthy, K.,** and **Howarth, J. C.:** Arch. Dis. Child., **28,** 110, 1953.
8. **Krebs, E. G.:** J. Lab. & Clin. Med., **31,** 85, 1946.
9. **Prasad, A. S.,** and **Koza, D. W.:** Ann. Int. Med., 41, 629, 1954.
10. **Rundles, R. W., Cooper, G. R.,** and **Willett, R. W.:** J. Clin. Invest., **30,** 1125, 1951.
11. **Sanford, J. P., Favour, C. B.,** and **Tribeman, M. S.:** Clin. Res. Proc., **2,** 29, 1954.
12. **Saslaw, S.,** and **Wall, R. L.:** Proc. Cen. Soc. Clin. Res., **27,** 111, 1954.
13. **Wyngaarden, J. B., Crawford, J. D., Chamberlin, H. R.,** and **Lever, W. F.:** Pediatrics, **9,** 729, 1952.
14. **Young, I. I.,** and **Wolfson, W. Q.:** Clin. Res. Proc., **2,** 101, 1954.
15. **Zinneman, H. H.:** Medical Grand Rounds, V. A. Hosp., Minneapolis, **11,** 12, 1953.
16. **Zinneman, H. H., Hall, W. H.,** and **Heller, B. I.:** J. Am. Med. Assn., **156,** 1399, 1954.

CLINICAL PATHOLOGICAL CONFERENCE

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A 14-year-old white male was admitted to the Northern Division of Philadelphia General Hospital on February 26, 1954, with a chief complaint of "headache, backache, sore throat and vomiting" of 2 days' duration. The patient was apparently well until February 24, 1954, when his illness began with a sore throat and vomiting, followed by dull, constant, frontal headache, lumbar backache, nuchal rigidity and malaise. These symptoms became more severe and the family physician made a diagnosis of poliomyelitis, so that the youngster was subsequently referred to the hospital. As a child the patient had had measles, mumps, chickenpox and whooping cough, but there was no history of diphtheria, scarlet fever, or rheumatic fever. At the age of 3 he sustained a brain concussion as a result of an automobile accident and was unconscious for several hours. The family history revealed that several members of the family had died of pulmonary tuberculosis. The systemic review and the social history were non-contributory.

Physical examination on admission revealed a well developed, well nourished, adolescent male looking extremely pale and acutely ill. The rectal temperature was 98.4° F., the pulse was 74 and regular, the respirations were 22, and the blood pressure was 150/90. There was tenderness over the right supraorbital ridge which was accentuated by percussion. The pupils were equal, regular and reacted well to light and in accommodation. The extraocular muscles were intact. Fundoscopic examination revealed normal discs, and no hemorrhages or exudates were present. The ears and nose were not remarkable. The lips were dry and cracked, and numerous small petechiæ were seen over the hard and soft palates. The tongue protruded in the midline and there were exudate patches present on the pharynx. The gag reflex was present. The lungs were clear to percussion and auscultation. The heart was not enlarged, a normal sinus rhythm of 74 was present and no murmurs were heard. Abdominal examination was not remarkable. The cranial nerves were intact and the sensory modalities of position and pain were normal. All the deep tendon reflexes were hyperactive but equal bilaterally. The cremasteric reflex was present bilaterally. The Kernig and Brudzinski signs were positive bilaterally and nuchal rigidity was present. On the back of the hands were present mul-

tiple lesions diagnosed as spider angiomata.

LABORATORY STUDIES. The hemoglobin on admission to the hospital was 14 gm. The total white blood cell count was 12,800, with 78% neutrophils and 22% lymphocytes. On March 4, 1954, the hemoglobin was 14.1 gm. and the white blood cell count had dropped to 9,650. The differential count was the same. On the same day the platelets were 272,000, the bleeding time was 2 minutes and 20 seconds and the clotting time 4 minutes and 45 seconds. On admission, the specific gravity of the urine was 1.018, and 5 days later was 1.021. A trace of albumin was present on both occasions. The blood urea nitrogen was 22 mg. per 100 cc., and the blood sugar (non-fasting) was 78 mg. Serological tests for syphilis were negative. Three lumbar punctures were performed. On February 26, the initial pressure was 80 and the fluid was grossly bloody. A total of 158 white cells were present, with lymphocytes 78% and neutrophils 22%. On March 1, the inital pressure was 100 and the fluid was xanthochromic. On March 4, the inital pressure was 250, the fluid was xanthochromic, and 23 white cells were present, all of which were lymphocytes. A total of 2,040 red blood cells were present. Spinal fluid culture showed no growth. Liver function studies included the cephalin flocculation, thymol flocculation, thymol turbidity, total cholesterol and esters, and bromsulphthalein retention, all of which were within normal limits. A nasopharyngeal culture grew out *N. catarrhalis* and non-hemolytic streptococcus. The PPD, first strength, was negative.

HOSPITAL COURSE. A lumbar puncture was performed on admission and spinal fluid and throat cultures planted. The patient was given 5 gm. of sulfadiazine immediately by vein and then 1 gm. every 4 hours. Crystalline penicillin, 1,000,000 units, was given every 3 hours without improvement in 24 hours. Thereafter, the medication was discontinued. On February 28, the headache became more severe and began radiating to the occipital region. The next day repeat fundoscopic examination disclosed papilledema. A neurological examination revealed a relatively alert patient, definite photophobia, marked nuchal rigidity with bilateral Kernig and Brudzinski signs and slight left central facial palsy. On March 3, the patient was transferred to the Blockley Division of the Philadelphia General Hospital. On admission the temperature was 98.6° F. rectally, the pulse was 72 and regular, respirations were 24 and the blood pressure was 160/100. There was marked papilledema. The apex of the heart was felt in the anterior axillary line in the 5th intercostal space. A soft systolic murmur was heard over the entire precordium, loudest at the apex. No facial palsy was thought to be present, but the tongue deviated to the right. The remainder of the physical examination had not changed. The following day neurological examination detected slight frontal bossing and dilated temporal veins. The lumbar puncture was repeated. On March 8, the patient developed diplopia. Reexamination at this time revealed a grade II systolic blowing murmur heard over the precordium but loudest in the pulmonic area. A day later the patient became lethargic and again complained of photophobia. On March 10, the nurse found the patient crying and in a very apprehensive state. He had a nose bleed. The blood pressure at this time was 180/120 and the rectal temperature was 101° F. The left side of the body was areflexic. The right pupil was dilated. During the examination both pupils dilated and the patient became incontinent of urine and feces. Mild clonic contractions began on the

left side. His respirations became sterterous and then irregular in rhythm. Thirty minutes later, respirations ceased and the patient became cyanotic. Artificial respiration and caffeine sodiobenzoate were given. He was given 50 cc. of 50% glucose intravenously at 4:30 p. m. followed by 100 cc. of 30% glucose at 5:45 p. m. The eye grounds showed 6 diopters papilledema and hemorrhages appeared in the right retina. The patient meanwhile had been placed in a respirator and had become acyanotic. At 6 p. m. the blood pressure was 190/120 and subsequently rose to 210/120, with a pulse of 100. At 6:35 p. m. on March 10, 1954, the patient expired.

Dr. Gyorgy: The Clinical Pathological Conference today is to some extent a simple problem and on the other hand a complicated one. There is no question that we are dealing with a space taking "something" in the brain and death was due to intracerebral "something." The patient, from the beginning, had a high blood pressure and right before death it rose to 210/120. All the neurological examinations were consistent with greatly increased intracranial pressure.

First, I would like to discuss a few points which are in this protocol. I would like to point out a few pertinent facts and a few which are misleading.

This white child became sick on February 24, with a sore throat, vomiting, and headache; therefore, I think first of all of infection as the best diagnosis. He had nuchal rigidity and weakness, central nervous system involvement and naturally with these symptoms one thinks of meningitis. He had an injury at the age of three with unconsciousness for several hours; this may well be a red herring.

When the child came into the hospital he had numerous small petechiæ over the palate. The tongue protruded in the midline. When you have a child with an acute disease, sore throat and petechiæ, you think of meningococcus infection. However, I am not satisfied with this diagnosis. He never had fever, was not in shock and he was not a very sick child. He should have had fever and the petechiæ described were only over the palate. The spinal fluid was negative. I am a little doubtful about meningococcal meningitis or meningococcemia.

We have a familial history of several deaths due to tuberculosis. Could he have had a tuberculous meningitis with block causing death in 14 days? Tuberculin test was negative; however, in miliary tuberculosis this is very possible. We often see negative tuberculin tests in far advanced tuberculosis.

He had some localization in the right hemisphere with tenderness over the right supraorbital region. Could this have been an abscess or a hematoma? I do not think so, because we have no signs such as fever, nothing in the history to suggest infection and no signs in the spinal fluid. Could this be renal thrombosis? We have no other signs to indicate it. There was no fever and no history of infection, injury or dehydration. His heart became enlarged, with a blowing systolic murmur developing, and the apex was in the anterior axillary line. Perhaps this was produced by thrombosis or embolism. Could this be subacute bacterial endocarditis? I do not think so, because the hemoglobin was 14 and remained at 14. With subacute bacterial endocarditis there should have been some anemia and other embolic phenomena. I would like to know if Dr. Ostrum sees any signs of tuberculosis, increased intracranial pressure; and what is the size of the heart?

Dr. Ostrum: We have two studies, one of the chest and the other of the skull. The skull studies show normal

outline of the pituitary fossa and the skull is normal in size. There is some evidence of increased intracranial pressure. The sutures are slightly widened and there is some thinning of the internal plates. Examination of the chest shows a normal outline of the lungs. The pulmonary vessels are not enlarged. The heart shows considerable enlargement of the left ventricle and there is some enlargement of the ascending aorta. The aortic knob and descending aorta are extremely small.

DR. GYORGY: The skull film was taken on March 4, and the patient developed increased intracranial pressure during the last few days. He had hemorrhages of the retina on the right. I am satisfied that he had no tuberculous infection visible and no miliary tuberculosis. We are left with two possibilities and probably neither is correct. A disease which from February 14 to March 10, would end fatally is a very acute disease.

In my opinion the best possibilities are hemorrhages going back to injury at age of 3, with vessels injured and aneurysm developing, with hemorrhage in the right frontal lobe and pressure on the third and twelfth nerves, which would explain the pupil size and deviation of the tongue. This is my first diagnosis. It is supported by lack of signs of infection; no fever, no leukocytosis except on the first study, and the normal hemoglobin. No bacterium was found and I assume the blood cultures were also negative. The absence of any sign of infection is against meningitis and tuberculosis. Even though he had an enlarged heart developing with hypertension, I am considering it not a sign of congenitial heart. I would rather, on the basis of a normal hemoglobin, not entertain a diagnosis of subacute bacterial endocarditis with embolism. Acute endocarditis with bacterial thrombi is a possibility. It is difficult to explain what in 14 days caused the acute fatal course with signs of increased intracranial pressure.

My second possible diagnosis would be brain abscess which includes also emboli. A point which has been stressed in the history twice is that of the liver function tests, because of spider angiomata on the back of the hand. I think they are red herrings. Spider angiomata are very rarely over the back of the hands. They are usually in the upper part of the body. Being over the back of the hands, only, did not impress me as a manifestation of liver disease.

In summary, we have a white male child with upper respiratory disease, developing a fulminating course, with central nervous system involvement with something in the right hemisphere. My diagnoses are (1) hemorrhage, (2) brain abscess, with emphasis on hemorrhage.

We see marked hypertension in brain tumor and one sign is acute hemorrhage. Clinically, blood pressure and pulse rate go up with intracranial pressure. The child never had any findings in his urine. The only explanation for the very high blood pressure with no changes in the urine is that of tumor.

DR. OSTRUM: I would like to describe the heart and aorta a little more in detail. I would like to call attention to the ascending aorta. It is considerably dilated. The left ventricle is enlarged and rounded, the type that is usually seen in some form of aortic stenosis. The aortic knob is extremely small and indefinite in outline. The descending aorta is inconspicuous, and just above the level of the main left pulmonary artery there is a definite indentation in the descending portion of the aorta. The ribs are normal.

DR. GYORGY: One cannot make a diagnosis if one does not have the facts. This new information leads to coarcta-

tion of the aorta and this would explain why the blood pressure was 150 on admission and why it always remained high, because of long standing coarctation of the aorta. Now we have two possibilities: The hypertension became so marked as to lead to hypertensive encephalopathy; or second, he had endocarditis, or again still rupture or hematoma. The fact that we now have a diagnosis of coarctation brings us back to a congenital heart lesion. It is unfortunate that blood pressures were not taken in the lower extremities of this child, nor were the femoral pulses palpated. It becomes very apparent that one should consider both these simple procedures in the physical examination as mandatory in children and adults, whether hypertension is present or not. This is no longer done for the sake of completeness or didactic purposes. The present status of cardiovascular surgery allows the repair of congenital defects in a great number of patients and allows their subsequent return to useful living. The absence of femoral pulses or decreased blood pres-

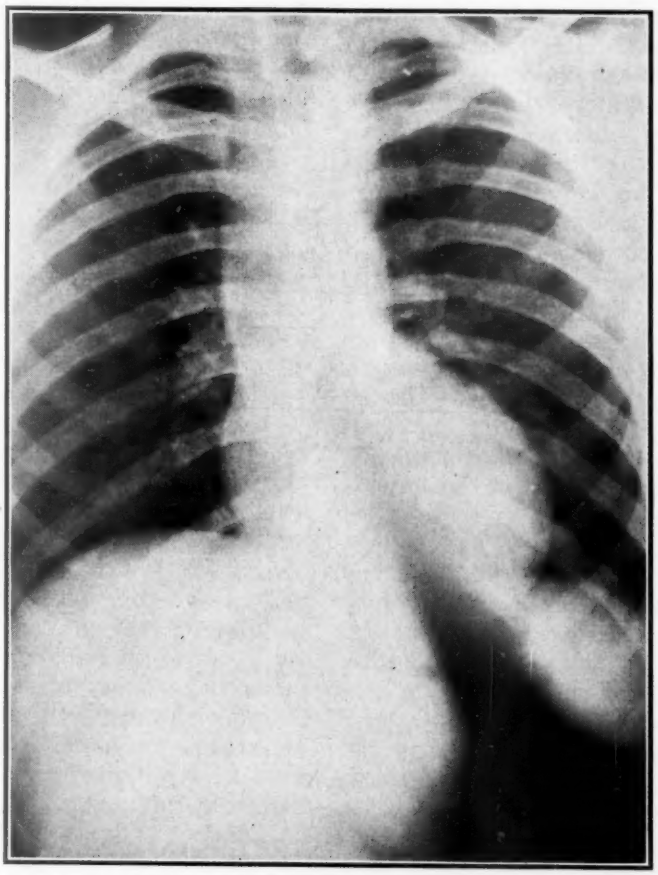

Fig. 1.—(1) Enlargement of left ventricle. (2) Dilated ascending aorta. (3) Inconspicuous aortic knob and descending aorta. (4) Indentation or dimpling in the descending aorta just above the left pulmonary artery.

sure in the lower extremities, therefore, becomes a diagnostic sign of utmost importance and must never be overlooked. Therefore, I have a slight change to make after receiving the necessary information. The diagnosis is coarctation of the aorta with hypertension.

DR. BRODY, PATHOLOGIST: Examination of the great vessels revealed marked dilatation of the root of the aorta, the ascending aorta and the arch. quarter the size of the proximal portion of the aorta. Distal to the constriction, which involved the entire aortic wall, the aorta dilated again but never quite approached the normal aortic caliber. There was no prominence of the intercostal arteries, but the internal mammary arteries were definitely increased in size. The heart weighed 250 gm. There was marked hypertrophy of the left ventricular wall. There were no other valvular or congenital lesions

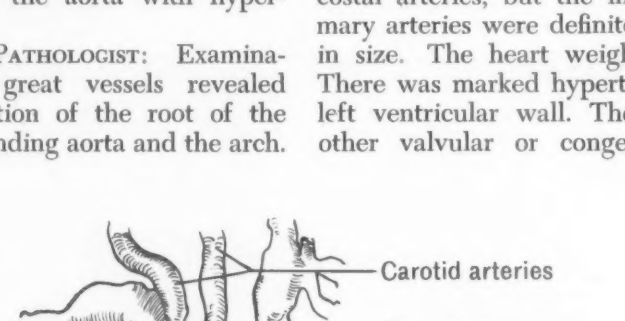

Fig. 2.

The innominate artery was not remarkable; it was normally situated and the configuration was normal. The left common carotid artery was not remarkable. There was great increase in width and circumference of the left subclavian artery. The ductus arteriosus (ligamentum Botallo) was well visualized. It was firm, sclerotic, and not patent. Just distal to the ductus was present a constriction of the aorta, narrowing the aortic lumen to one present. Both kidneys grossly were of normal size, shape, color and consistency. Microscopically, there were no lesions consistent with hypertensive cardio-renal disease or pyelonephritis.

Examination of the brain was made by Dr. Helena R. Riggs. It revealed a very large cerebellar pressure cone; massive subarachnoid hemorrhage was present over the convexity and the vertex on the right. Source of the bleeding was a leaking miliary aneurysm located

at the main bifurcation of the right middle cerebral artery high in the Sylvian fissure. The aneurysm measured about ½ cm. in diameter. Dissection of the circle of Willis revealed an extremely short and hypoplastic anterior communicating artery and posterior communicating artery on the right. The entire circle was extremely thin-walled and showed no atheroma. Section of the brain showed massive hemorrhage into the subcortical white matter of the posterior, frontal and parietal lobes.

Two points in this case may merit some further discussion. The first is the fact that several examiners during life noted "spider angiomata" to be present in this youngster. Bean[1] has emphasized that spider naevi may occur in patients without liver disease, as may have occurred in this patient. They have been known to occur in perfectly normal individuals. They may also occur in pregnant women appearing first around the second to the fifth month and disappearing soon after delivery. The lesion itself is located mostly around the face, neck, and upper portion of the chest, rarely occurring below the diaphragm. They may also occur in the mucous membranes of the nose, mouth, pharynx, hard and soft palates and the alimentary canal. Clinically, they have a body and legs and a surrounding erythema. Lesions may be seen to pulsate on compression. The temperature over the structure may be three degress higher than over the surrounding skin. The color is a fiery red. Histopathologically they may consist of an overgrown end artery or a thick coiled artery in the subcutis with an abrupt thinning of the walls forming a vein-like chamber.

Other lesions may be confused with spider angiomata. The first is a venous star. It occurs over the lower borders of the ribs, on the dorsum of the feet and lower legs and above the knees on the medial aspect of the thigh. The venous stars occur when there is a persistent elevation of venous pressure. They may be blue or bright red. The skin temperature is not increased over these lesions. Histopathologically they consist of dilated veins. Another entity may be familial hemorrhagic telangiectasia. This lesion occurs more often on the upper portions of the body, but may occur anywhere on the skin. They may occur in the nasal vestibule, tip of the tongue, palate, pharynx or esophagus. They are punctiform and flat or may be slightly elevated. Pulsation is hard to demonstrate. The skin temperature is not elevated over the lesions. Hemorrhage from these lesions may be mild or severe but a history of bleeding in the family is invariably obtained. Histopathologically there is a thinning of the wall of the vessel, loss of muscle and elastic tissue and development of tortuous coiled masses of tiny aneurysmal vessels composed of capillaries, arteries and veins. The last confusing lesion is the cherry angioma. This is most commonly found over the trunk, rarely occurring on hairy portions of the body. It is more common in elderly individuals. The lesions are usually flat but may become dome-like and even pedunculated. No pulsation is seen here and the skin temperature over the lesion may be slightly decreased compared to the surrounding skin. Histopathologically they appear as numerous dilated vascular channels.

The other thing that one should mention is the relationship between coarctation of the aorta and cerebral aneurysms. Woltman[6], Green[3], O'Reilly[4], and Reifenstein[5] all call attention to this association. At the Johns Hopkins Hospital, Berthrong[2] made a study of 162 cases of congenital heart disease. Of 10 patients with coarctation of the aorta 4 had aneurysms of the

circle of Willis and in 3, death was caused by massive subarachnoid hemorrhage.

The FINAL DIAGNOSIS was:

CHIEF DISEASE: Coarctation of the aorta (adult type).

CAUSE OF DEATH: Subarachnoid and intracerebral hemorrhage due to leaking miliary aneurysm of the right middle cerebral artery.

DR. OSTRUM: A most important Roentgen-ray sign in coarctation of the aorta is notching of the ribs. In the absence of rib notching, other signs may be of great help as the dilated ascending aorta, the small inconspicuous descending aorta and aortic knob, the indentation or dimpling in the descending aorta just above the left pulmonary artery, the density in the left apex and left mediastinum, produced by the enlarged left subclavian artery, and the nodular densities beneath the sternum in the lateral view of the chest, produced by the enlarged internal mammary arteries. The characteristic hypertrophy of the left ventricle is also important.

REFERENCES

1. **Bean, W. B.:** Circulation, **8**, 117, 1953.
2. **Berthrong, M.,** and **Sabiston, D. C., Jr.:** Bull. Johns Hopkins Hosp., **87**, 384, 1951.
3. **Green, F. H. K.:** Quart. J. Med., **21**, 419, 1928.
4. **O'Reilly, J. N.,** and **Chapman, O. W.:** Arch. Dis. Child., **18**, 109, 1943.
5. **Reifenstein, G. H., Levine, S. A.,** and **Gross, R. E.:** Am. Heart J., **33**, 146, 1947.
6. **Woltman, H. W.,** and **Shelden, W. D.:** Arch. Neur. & Psychiat., **17**, 303, 1927.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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LABYRINTHINE (VESTIBULAR) FUNCTION TESTS

I. TECHNIQUES

BY A. HARRY NEFFSON, M.D.

DISTURBANCES of the vestibular mechanism result in symptoms which impel the patient to seek the advice of a physician. The predominant symptom is usually vertigo or dizziness. Since this symptom is so commonly an expression of many diverse affections, it is very often difficult for the physician to evaluate its importance when attempting to make a differential diagnosis. Among the conditions resulting in vertigo the following can be briefly listed: Ménière's syndrome, labyrinthitis associated with acute and chronic infections, labyrinthine hemorrhages due to various blood dyscrasias and physical trauma, so-called toxic labyrinthitis due to alcohol, foods and medicaments, cardiac and circulatory insufficiencies, various diseases and tumors of the central nervous system, hereditary degenerative diseases, and many other rarer affections.

Because of this wide variation of clinical conditions which are characterized by labyrinthine vertigo, it is often necessary to obtain information regarding the functional activity of the eighth cranial nerve and its end organs before one can establish the correct diagnosis. For a better understanding of the basis, techniques, and interpretation of the tests used to assay vestibular function, a short review of the anatomy and physiology of the labyrinth and the associated structures will be helpful.

ANATOMY. Relatively recent investigations have added considerably to our knowledge of the vestibular structures and their functions. These studies entailed difficult dissections of minute structures and complicated physiologic experiments and chemical examinations.

The labyrinth consists of an *auditory*

portion, the cochlea, and possibly the saccule, and a *non-auditory* or vestibular portion, the three semicircular canals and the utricle. These structures are all located in the petrous portion of the temporal bone. The bony labyrinth is composed of three distinct layers of bone, periosteal, enchondral, and endosteal. There are three semicircular canals in each ear, two vertical, the anterior and posterior vertical canals, and one external or horizontal canal. One end of each canal is dilated forming what is known as the ampulla, and each canal communicates at both extremities with the utricle, the non-ampulated ends of the vertical canals first joining at the crus commune, so as to communicate through a common orifice with the utricle. Thus, five communications are established with the vestibule, a relatively spacious chamber lying medially between the canals and the cochlea. The semicircular canals are situated in planes at right angles to each other and are placed so that on each side of the head there are two canals in the same plane, but with the ampulla in opposite directions. The posterior vertical canal is parallel to the long axis of the petrous pyramid and the anterior vertical canal is at right angles to it. Thus the anterior vertical canal lies in approximately the same plane as the posterior vertical canal of the opposite side. The external canal, often called the horizontal canal, does not lie in a horizontal plane, but slopes posteriorly at an angle of about 30 degrees.

On the medial wall of the bony vestibule are two depressions, an elliptical one for the utricle which lies in a horizontal plane and a spherical depression for the saccule which lies in a vertical plane. Perforations for nerves to the maculas of the utricle and saccule and the ampullas of the semicircular canals are present. Also in the bony wall of the vestibule are found openings for the oval and round windows, which conduct sound vibrations from the middle ear, and for the endolymphatic duct and cochlear aqueduct, which are concerned in the circulation of the endolymphatic fluid. The saccule communicates with the utricle and with the cochlea through the duct of Hensen.

Within this bony labyrinth lies a membranous replica, separated from the bony wall by the perilymphatic fluid, which is thought to be connected with the cerebrospinal fluid system via the aquaeductus cochleae (Lempert, Meltzer, Wever, Lawrence and Rambo[70]). The membranous labyrinth is filled with endolymphatic fluid, which is thought to be produced in the cochlear portion and absorbed through the walls of the endolymphatic duct (Lindsay[72]). The membranous labyrinth, although afloat in the perilymphatic fluid, is moored to the bony labyrinth at the points of entrance of the nerves and is also loosely attached by scattered fine septa.

The receptor organ of the semicircular canals is situated in each ampullated end and is called the crista acoustica. It consists of a ridge, at right angles to the long axis of the canal, which is covered with a specialized neuroepithelium, the sensory hair cells of which project into a gelatinous dome-shaped structure known as the cupula. The cupula rises like a hinged door to the roof of the ampulla and is free to move with the flow of endolymph in either direction. In the wall of the utricle are the five openings of the semicircular canals, one opening for the cochlear aqueduct and another for the ductus endolymphaticus, which communicates with the saccule. The sensory organ of the utricle is called the macula. This consists of a plaque of hair cells covered by a gelatinous layer

on which are small concretions of lime salts called otoliths. This macula and its counterpart in the opposite ear lie in the same plane, which is approximately horizontal. The sensory organ of the saccule is also called the macula and its construction is similar to that of the macula of the utricle. It lies approximately in a vertical plane and the planes of the two saccular maculas form an angle opening forward and downward.

Blood Supply. The internal auditory artery, a branch of the basilar artery, supplies the entire membranous internal ear. It divides into three branches: the vestibular, vestibulocochlear and the cochlear arteries. The venous drainage is through the internal auditory vein, the vein of the cochlear aqueduct and the vein of the vestibular aqueduct. The disadvantage of the end artery circulation in the labyrinth has been emphasized by Hilger[50]. He has also postulated many sympathetic and parasympathetic interrelations to explain some syndromes of internal ear disturbance. However, since detailed knowledge of the sympathetic and parasympathetic nerve distribution within the internal ear is still meager, the proof of these assumptions must await further study.

Neural Pathways. Impulses received from the receptors of the various structures of the nonauditory labyrinth are conveyed to the brain over the vestibular branch of the eighth cranial nerve. The cell bodies of these nerve fibers lie in Scarpa's ganglion. Their dendrites are distributed to the hair cells of the vestibular receptors and their axons go to the vestibular nuclei of the medulla, a few going directly to the cerebellum. As it leaves the internal auditory meatus, the vestibular nerve runs together with the acoustic and facial nerves until they reach the medulla; from there they diverge.

Many details about the exact intracranial connections of the labyrinth are as yet unknown, because it has not been possible till very recently to produce separate lesions of the individual end organs so as to permit studies of nerve degeneration. In general, branches of the vestibular nerve go to four nuclei in the medulla (Brodal[19]). These are the descending (or vestibulospinal or inferior) nucleus, the lateral vestibular nucleus (Deiters), the medial or triangular nucleus (Schwalbe), and the superior triangular nucleus (Bechterew). After leaving these nuclei, branches of the vestibular nerve are widely distributed throughout the brain. A large number go to the cerebellum. From here, relay fibers pass into (1) the vestibulo-spinal tract or over the spinal extension of the medial longitudinal fasciculus to the upper cervical region of the spinal cord for reflex connection with the body musculature; (2) the vestibulocerebellar tract to the superior cerebellar peduncle and then to the cerebrum, conveying the sensation of vertigo; (3) the vestibulo-ocular tract for connection with the external ocular nuclei to control the movements of the ocular muscles (it was formerly thought that most of these fibers passed through the posterior longitudinal bundle, but recently Lorente de Nó[73] and Spiegel and Sommer[95] have shown that there are also pathways from the vestibular nuclei to the external ocular nuclei through the substantia reticularis); and (4) other fibers connect with the autonomic nervous system providing reflex pathways responsible for the perspiration, nausea, vomiting, and change in pulse which occur during labyrinthine stimulation.

Although the labyrinth has widespread cranial connections, it has been shown that only part of the brain stem is essential for performing the known

vestibular reflexes. Thus, if a transection is made through the rabbit's brain just above the red nuclei, all known vestibular reactions can still be elicited (Magnus and de Kleyn, see McNally and Stuart[83]). The essential part of the central nervous system for vestibular nystagmus seems to be that part of the brain stem situated between the oculomotor nuclei above and the vestibular nuclei below. If a transection is made just above the nuclei of the abducens nerves, a horizontal nystagmus can still be obtained.

PHYSIOLOGY AND FUNCTION. *The Labyrinth.* The function of the labyrinth is to assist in maintaining balance by stabilizing the position of the eyes, the head and the body. It reacts to the slightest movement of the body or change in posture through the functioning of the various vestibular receptors, as they are stimulated by the movement of the endolymph. These stimuli, in turn, are translated by the central nervous system into kinetic sensations.

The Saccule. The function of the macula of the saccule is not clearly known at the present time and there are no clinical methods to test its proper functioning. It had been thought (Quix[90], Magnus[78]) that static labyrinthine reflexes were derived from both the utricle and the saccule. However, later experiments (McNally and Tait[84] and Versteegh[106]) indicated that the saccule has no vestibular function. Experiments by Ashcroft and Hallpike[5] on the frog have suggested that the saccule is a vibration receptor. Löwenstein and Roberts[75], working on the thornback ray, found the saccule to respond to low-frequency vibrations and gravity changes. Ledoux[65] stated that the saccule of the frog responds to vibratory stimuli, but not to gravity changes or acceleration. However, Jongkees[57] in experiments on the rabbit thought that the saccule may be stimulated by linear acceleration.

The Utricle. Many workers (Breuer[16, 18], Kreidl[61], Versteegh[106], Ulrich[101], Tait and McNally[99], Ross[92], and others) have shown that the function of the utricular maculas is to respond to gravitational forces, as opposed to rotatory movements. Although the exact mechanism of otolithic stimulation is still obscure, it has been postulated that motion which exerts a gravitational pull on the otolithic membrane away from the hair cells stimulates the utricular maculas. Maximal stimulation is apparently obtained when the maculas are horizontal and the otoliths rest on the hair cells. Experiments have also established that the otolithic organ of the macula reacts both to linear acceleration and to tilting. Clinical tests of the utricle (tilting tests) have been described by Grahe[47], but have never been generally adopted. Fitzgerald and Hallpike[40] suggested that some phases of the nystagmus resulting from labyrinthine stimulation were due to stimulation and response by the utricle, but they did not confirm this assumption by animal experimentation. The electrical activities of single nerve fibers were recorded in the frog by Ross[92], in the dogfish by Löwenstein[74], and in the frog by Coppée and Ledoux[26]. They all reported that the utricle responds to gravitational stimuli. Ross[92] and Löwenstein[74] found that the utricle responded to linear acceleration, and Löwenstein[74] and Coppée and Ledoux[26] reported that the utricle responded to vibration.

The Semicircular Canals. The function of the semicircular canals has been quite well established as a result of difficult and painstaking experimental work. One of the first to associate vertigo with the labyrinth was Ménière, in 1861. Goltz[45], in 1870, suggested that the function of the laby-

rinth is to maintain body balance. Mach[77], Breuer[16], and Crum Brown[27] independently elaborated on the mechanism of labyrinthine action. Flourens, in 1842, and Ewald[37], in 1892, analyzed the effects of semicircular canal stimulation, thus helping to establish rules for the interpretation of semicircular canal responses. Bárány[8], in 1907, developed the rotation and caloric tests so as to make them clinically practical. Sherrington[94] made a great contribution by analyzing labyrinthine reflexes and showing their relationship with other parts of the central nervous system. Steinhausen[96,97] and Dohlman[32] working with living fish established experimental proof of the movement of the cupula in the direction of the movement of the endolymph. By inserting a droplet of opaque oil into a semicircular canal and then subjecting it to acceleration, photographs demonstrated the movement of the endolymph and corresponding deviation of the cupula. It was found[96] that the cupula has a natural vibration period of about 20 seconds; that is, it returns to its normal position in about 20 seconds after deviation, provided the acceleration or deceleration has been stopped. Tait and McNally[99] grouped the canals into a gravity set (the 4 vertical canals) and a nongravity set (the 2 horizontal canals). By cutting the nerves to the various canals in the frog they[99] found that when a canal is stimulated it results in an extension of the limbs on its own side and flexion of the limbs on the opposite side. Thus, each canal seems to be connected with the body musculature of both sides in order to accomplish a definite pattern of protective reactions. They[99] also noted that when the utricles in the frog were removed, there was increased response to stimulation on the part of the vertical canals. By removing one utricle at a time they found that the utricle on one side is connected with and restrains the vertical canals of the opposite side. Ross[92] recorded the action potentials from individual ampullary nerve fibers in the frog; Adrian[1] recorded the electrical activity of the vestibular apparatus in the cat; Löwenstein and Sand[76] (1940) in the elasmobranch; Maxwell[80] (1923) in the dogfish; Ledoux[66] (1951) in the frog; and Van Eyck[104] (1951) in the pigeon. Their findings, though basically similar, are not in accord on some points. For example, Löwenstein and Sand[76] and Ledoux[66] found that the saccule responds to gravity in addition to that of vibration, and the utricle responds to vibration in addition to that of gravity. Van Eyck[104] reported that the semicircular canals responded to vibration as well as to acceleration. Löwenstein and Sand[76] and Ledoux[66] reported responses from each semicircular canal in the dogfish and in the frog by turning in a clockwise and counterclockwise direction, whereas Ross[92] found responses in the frog to turning in only one direction. It is evident that caution must be exercised when drawing conclusions based solely on the electrical responses of single nerve fibers.

BASIS OF LABYRINTHINE FUNCTION TESTS. Any movement of the head causes a flow of the endolymph within those semicircular canals which happen to be in the same plane as the movement of the head. Also, the natural inertia of the endolymphatic fluid causes it to lag behind at the start of any movement of the head and to continue to move on after the head movement has ceased. This flow causes the receptor nerve endings in the ampulla to bend and thus be stimulated. This stimulus results in certain patterns of reflex movements of the eyes and body muscles which are designed to retain the field of vision and to recover

or maintain the body equilibrium. Since it would be highly impractical to test the functioning of the individual semicircular canals in the same manner in which they function normally, experiments were undertaken in which abnormal types of stimuli were applied to individual semicircular canals, and from the effects of this stimulation certain rules of interpretation were laid down.

Laws of Flourens and Ewald. In 1842, Flourens, working with pigeons, noted that when a semicircular canal was stimulated or injured, the resulting nystagmus was in the same plane as the stimulated or injured canal. When more than one canal was stimulated, the reaction was in a plane corresponding to the resultant of the separate forces involved. On the basis of these observations, otologists later formulated the law of Flourens: "Each semicircular canal is responsible for nystagmus in its own plane."

Ewald[37], also working on pigeons, drilled a fistula in the bony wall near the ampulla of the semicircular canal and by means of a "pneumatic hammer" he produced alternately positive or negative pressure producing endolymph movement toward or away from the ampulla. He noted that a movement of the endolymph toward the ampulla of the horizontal canal elicited a greater reaction than a flow away from the ampulla. On the other hand, the opposite effect was noted in the vertical canals, namely, a flow away from the ampulla was a more effective stimulus than one toward the ampulla. Van Eyck[104], in 1951, recording action currents from individual ampullary nerve fibers in the pigeon, confirmed the findings of Ewald[37]. Some workers[62,64,68,69,80,84,92,96,100] have found that in the lower animals (reptiles, amphibia, fish) semicircular canals react to stimulation in only one direction, that causing maximal stimulation.

On the basis of these experiments by Ewald[37], otologists formulated three laws to which his name is attached: Ewald's Laws: 1) In the horizontal semicircular canals maximal stimulation is produced by a movement of the endolymph toward the ampulla. Minimal stimulation results from a movement away from the ampulla.

2) In the vertical semicircular canals maximal stimulation is produced by a movement of the endolymph away from the ampulla. Minimal stimulation results from a movement toward the ampulla.

3) Maximal stimulation, of either the horizontal or vertical canals, elicits nystagmus with the quick phase to its own side. Minimal stimulation, of either the horizontal or vertical canals, elicits nystagmus with the quick phase to the opposite side.

Bárány[8] and others have assumed that these laws formulated from experiments on the pigeon are applicable also to the human labyrinth. However, in recent years some workers[24,25,73,103,108] have cast doubt on the validity of these laws as they apply to man. Based largely on calorigrams obtained by the technique of Fitzgerald and Hallpike[40] (which will be described later in this paper) Winston[108] concluded that Ewald's law is not physiologically valid in man. He deduces that when one labyrinth is altered or destroyed by disease or experimental surgery, the opposite vestibular apparatus also undergoes a change in function, so that Ewald's law then applies. This change in function, he asserts, is not due to alterations in the vestibular end organ, but is of central origin and is only a temporary state, until full central vestibular compensation becomes established. He[108] notes that Ewald's data were obtained after experimental ves-

tibular surgery had been performed and therefore these vestibular apparatuses cannot be considered as having functioned physiologically, but rather pathologically.

In general, however, these rules have proved to be a practical clinical guide in the interpretation of the effects of labyrinthine stimulation and they should continue to be used until further work is done to show that they need to be altered.

IMMEDIATE EFFECTS OF LABYRINTHINE STIMULATION. The effects of labyrinthine stimulation are manifested by characteristic eye movements, changes in the response patterns of the body musculature, reactions in the autonomic system, and even alterations of the sensorium. For the most part, our observations of these labyrinthine effects are concentrated on the character of the eye movements (nystagmus), the testing of the past pointing of the arms, and the description and duration of the sensation of dizziness. The occurrence of pallor, perspiration, nausea and vomiting is noted and rarely blood-pressure studies are made.

Nystagmus. This is a to-and-fro movement of the eyes, with other characteristics depending upon the originating cause, namely, whether the nystagmus is due to labyrinthine irritation, ocular disease or some central nervous system lesion. With labyrinthine irritation, for example, there is a slow movement, due to reflex ocular muscle action, and a rapid movement, due to compensatory cerebral response. The purpose of this compensatory reaction which originates in the central nervous system is the retention of a specific field of vision. Thus, it has been noted that during general anesthesia the quick component disappears, while the slow one remains (Quix[91], Wodak[110]). Curiously, the direction of the *rapid* movement is designated as the direction of the nystagmus.

Spontaneous Nystagmus. The presence of spontaneous nystagmus is most important. It is of the greatest significance when it occurs with the eyes directed straight ahead. A fine nystagmus can be overlooked unless considerable care is taken. Magnifying glasses or fundoscopic examination will often reveal the presence of a fine nystagmus which is not apparent to the naked eye. Spontaneous nystagmus may be caused by disease or irritation of any of the structures concerned in the production of the normal physiologic reaction; its origin may be vestibular, ocular or central. In passing, it should be remarked that excessive or prolonged use of the barbiturates can produce a spontaneous nystagmus.

Labyrinthine Nystagmus. Usually this is a horizontal, rotatory movement with a definite slow and quick phase. It is of small amplitude, short duration, and is often associated with cochlear dysfunction. When there is irritation of the labyrinth the quick phase is in the direction of the irritated side. When the labyrinth is destroyed, by disease for example, the quick phase is toward the healthy side, because there is no opposition from the other side. Usually, this type of spontaneous nystagmus is accompanied by vertigo and impaired hearing and lasts only a few weeks.

When labyrinthine stimulation is applied during the performance of function tests, the examiner watches for certain characteristics of the nystagmus, namely (1) the latent period, that is, the time of onset following the start of stimulation, (2) the direction, (3) the amplitude, (4) the frequency, and (5) the duration. It is not easy to measure the strength or amplitude of the nystagmus, and the methods which have been described do not

lend themselves to common clinical use (Wotzilka[113], Ohm[87], Kuilman[63], and Perlman and Case[89]). The frequency of the nystagmus can easily be given by a number, but the result varies in the same patient under the same set of circumstances (Fischer[38] and Woletz[112]).

Regarding the significance of the latent period there has been a lack of agreement. Cawthorne, Fitzgerald and Hallpike[24,25] and Barbey[11] feel that it is not of much value, because it is strongly influenced by the bony structures of the petrous bone. Both Jongkees[55] and Arslan[3] doubt the clinical value of this period because it depends mainly on anatomic factors, rather than on the peripheral vestibular apparatus. Brunner[21], on the other hand, considered the latent period important as an indication of an alteration in the excitability of one labyrinth (Brunings[20]). Wodak[110] also maintains that the latent period is important and helpful diagnostically in distinguishing between a normal and a hyper- or hypoexcitable labyrinth. Atkinson records the time of the latent period, and compares it with the duration of the nystagmus. He stresses the importance of the numerical relationship between the two time periods, rather than the actual times themselves. This will be discussed more fully later in the paper. Certainly it would seem to be of value when comparing the labyrinths in the same individual, since any difference in the petrous bones or ear canals would be negligible, except in occasional rather easily recognizable cases.

The duration of the nystagmus is generally considered to be the most useful index by which to judge the results of caloric or rotatory stimulation of the labyrinth.

Some workers have advocated the use of biconvex glasses of Frenzel[41], both to inhibit fixation of the eyes and to magnify their movements for easier detection.

Hertz and Riskaer[49] feel that a quantitative investigation of the vestibular function requires registration of the nystagmus. This has been done by several workers. Ohm[88], in 1924, attached to the sclera of the eye small hooks carrying a pen which recorded on a kymograph. Buys and Rijlant[23], in 1939, used a pneumatic system. Dohlman[33], in 1935, attached a small mirror to the sclera and recorded nystagmus photographically. Eye movements have also been recorded by means of a motion picture camera. Mechanical methods are uncomfortable for the patients and probably hinder the movements of the eyes. For optical recording it is necessary to have the eye illuminated, but nystagmus is inhibited by such illumination. None of these methods is adaptable to routine examinations.

Electrical registration was first described by Du Bois-Reymond[35] about 1850. Jung and Tönnies[58], in 1948, recorded the alterations of eye movements in the projection of the corneal-retinal potential picked up by electrodes attached to the face of the patient. Glorig and Spring[44], in 1950, recorded caloric nystagmus by means of an electroencephalograph. Hertz and Riskaer[49] have devised a method for the simultaneous electrical recording of nystagmus and voluntary eye movements, the sensation of turning, and the angular speed of rotation of the chair, in terms of degrees per second. Although this method is quite complicated, they maintain that it is of greater value in helping to localize a lesion of the vestibular apparatus than are other elaborate methods of testing, such as cupulometry.

Ocular Nystagmus. This is characterized by a to-and-fro oscillation, rather than by a slow and quick phase. It is

generally a horizontal movement, but occasionally it may be rotatory and rarely it is vertical. It is usually of long duration and is associated with some eye affection.

Optokinetic Nystagmus. This has been called train nystagmus and elevator nystagmus. The eyes follow a passing object (slow phase) and when the limit of eye movement has been reached, the eyes jerk back in the opposite direction (quick phase). Optokinetic nystagmus is affected by disease of the cerebrum, particularly in the region of the occipital lobes and their tracts to the brain stem nuclei. This type of nystagmus can be tested by placing the patient in the center of a slowly rotating drum. The inner surface of the drum is marked with alternate black and white vertical stripes. As the drum turns to the right there normally appears a quick phase of nystagmus to the left. This test is sometimes useful in distinguishing between some types of spontaneous nystagmus. For example, if there is a spontaneous nystagmus of labyrinthine or central origin, it is usually suppressed and the optokinetic nystagmus is superimposed, the direction being opposite to that of the turning drum. If, on the other hand, the spontaneous nystagmus is of ocular origin it often happens that the optokinetic nystagmus (opposite to the direction of the moving drum) does not develop. For more details of this test the reader is referred to Spiegel and Sommer[95], page 410.

Nystagmus of Central Origin. Spontaneous nystagmus which is vertical or oblique is usually indicative of disease of the central nervous system. Nystagmus which is in a different direction in the two eyes is always due to a central lesion.

Positional Nystagmus. This is a type of spontaneous nystagmus which appears when the head is held in a particular position. Moreover, it is often associated with vertigo when the head is placed in that position. It is important to ascertain the presence of this type of nystagmus, because it is a sign of organic disease either in the central or in the peripheral vestibular apparatus. Therefore, it is necessary to test for the presence of positional nystagmus when a patient complains of vertigo when holding his head in a certain position, or while lying in a certain position, or when looking in a certain direction. The examination should be made with the patient's head in various positions, namely: (1) with the head erect, (2) with the head turned on each side, (3) with the head in a hanging position, and then slowly rotated to one side and then to the other, and (4) while lying down (a) with the head back as in the supine position and (b) with the head forward as in the prone position. By getting the patient to sit up and placing his head in a hanging position, one may uncover a positional nystagmus which was not present previously. The type of nystagmus which occurs while changing the position of the head has been thought to be more often associated with a central lesion, such as in pseudo-Ménière's syndrome, cerebellar tumor, or multiple sclerosis (Nylén[86], Lindsay[71]). On the other hand, these workers felt that the nystagmus which occurs with the head held in only one position is more likely to indicate either a peripheral or a central lesion, such as a case of true Ménière's syndrome, a cerebellopontine angle tumor or a case of concussion involving central mechanisms. Jongkees[56] found that positional nystagmus occurred after the destruction or stimulation of the saccule of the rabbit and Gerlings[43] reported finding positional nystagmus in a group of patients with middle ear suppuration.

Nystagmus With "Directional Preponderance." Although this is not a type of spontaneous nystagmus, it would be best to describe it at this point. When a similar stimulus (hot or cold water or rotation) is applied to apparently normal labyrinths in the same individual and a stronger response is obtained toward one side as compared to the other, there is said to be a "directional preponderance" toward that side. In 1911, Bauer and Leidler (see de Kleyn and Versteegh[30]) reported that after removing the left cerebral hemisphere in the rabbit the postrotational horizontal nystagmus obtained after turning the animal to the right was much stronger than after the animal was turned to the left. When the right cerebral hemisphere was removed, the opposite effect was noted. They concluded that removal of one cerebral hemisphere causes the labyrinth on that side to become more excitable than that of the opposite side. These experiments were confirmed, in 1923, by Dusser de Barenne and de Kleyn[36]. They used alternate hot and cold caloric stimulation instead of rotation. They found that after removing one cerebral hemisphere the nystagmus that has the quick phase in the direction of the extirpated side is elicited more readily and is also stronger than the nystagmus toward the opposite, intact side. For example, when a right cerebral hemisphere was removed and cold water was applied to the left ear, with the head erect, the nystagmus to the right was of greater magnitude than when cold water was applied to the right ear, which produced a nystagmus to the left. In the same manner, stimulation of the right ear with hot water produced a greater reaction (nystagmus to the right) than did hot water stimulation of the left ear (nystagmus to the left). They concluded that there was a "Nystagmusbereitschaft" or as later translated by Fitzgerald and Hallpike[40], a "directional preponderance" to the extirpated side. In 1927, de Kleyn and Versteegh[30] found a "directional preponderance" in 11 patients who had a lesion of one cerebral hemisphere. In these patients there was a "directional preponderance" of the nystagmus to the side of the lesion. In 3 cases of cerebellar tumor they did not find this "directional preponderance." Fitzgerald and Hallpike[40] reported that they found a "directional preponderance" to occur more often when the disease was present in the temporal lobe, than when the disease occurred in other parts of the cerebral hemisphere. Later, Cawthorne, Fitzgerald and Hallpike[24,25] stated that they found "directional preponderance" in 21 out of 100 cases of Ménière's syndrome and that utricular disease was present. They found that the direction of the increased nystagmus was to the side opposite that of the diseased utricle. However, Jongkees[53] found "directional preponderance" in 20% of a series of normal individuals. Thus, the diagnostic significance of "directional preponderance" in a suspected case of Ménière's syndrome is still uncertain.

Past Pointing. In addition to the eye movements described above, labyrinthine stimulation produces definite response patterns by the body musculature. Physiologically, the labyrinth is stimulated by movement and these response patterns by the body musculature have as their purpose the preservation of the individual's balance. When the labyrinth is stimulated by disease or by abnormal artificial stimuli (caloric, electrical), these compensatory reactions are brought into play to adjust for a simulated movement, one which has not really taken place, and the result is upsetting to the patient. For purposes of clinical

study, examination has been limited mainly to the deviation of the arm movements, called "past pointing." As originally performed, the labyrinth was stimulated either by rotation or by caloric stimulation and the subject, his eyes shut, was told to raise his stiffened arm and then lower it so as to try to touch the examiner's finger with his own pointed finger. Normally, he will point to one side, that is "past point," to the side of the slow component of the nystagmus. The presence of past pointing and the side to which the patient points will depend upon the nature of the labyrinthine stimulus, the state of the vestibular apparatus and the condition of the cerebellum.

It might be noted here, in passing, that Bárány[10], in 1911, reported that synchronous arm movements were largely controlled by the cerebellum and that with cerebellar disease the symmetrical and synchronous movements of the arms were altered.

The significance of past pointing was stressed by Dorcus and Mowrer[34] as an involuntary, reflex compensatory reaction of the body musculature due to labyrinthine stimulation, and not a conscious corrective reaction to the vertigo as postulated by Jones[52].

Grahe[47] noted an advantage in having the patient move both arms at the same time. He pointed out that in a cerebellar lesion, the tendency to asymmetry of the arm movement is more striking. Dorcus and Mowrer[34] stressed the importance of not having the patient try to touch the examiner's finger during the test, because in so doing a voluntary act is introduced.

Before performing the caloric or rotation test the patient is shown how to move his arms, up and down, keeping the elbows stiff and the fingers pointing and the eyes closed. The patient is then told to perform these movements and the examiner watches for the presence of spontaneous deviations. After the labyrinth is stimulated the patient is told to move his arms in the same manner as he was taught. Normally, deviation of both arms occurs in the direction of the slow phase of the nystagmus, provided the stimulation of the labyrinth has been great enough. These tests are carried out not only with the head erect, but also with the head back so as to include all the semi-circular canals. To produce striking past pointing stronger labyrinthine stimulation is usually required, than is used in the minimal stimulation tests to be described later.

Subjective Sensations. The confusion in consciousness resulting from the conflicting visual kinesthetic and labyrinthine impulses during abnormal labyrinthine stimulation has been usually described as vertigo or dizziness. Although most patients with labyrinthine involvement have no difficulty in describing their sensations, McNally and Stuart[81] reported that after performing caloric tests, many patients stated that they did not experience any sensation of rotation; some had "a feeling of going to faint," "a swimming sensation," "a weakness," and others had difficulty in describing their sensations. Attempts have been made to distinguish between dizziness and vertigo as follows: Dizziness describes a sensation of movement within the head. Vertigo may be either subjective, in which the patient feels himself to be moving in space, or objective, in which the environment appears to be moving around him. However, for the most part the terms have been used interchangeably. The sensation of vertigo is usually in the direction of the quick phase of the nystagmus, opposite to the direction of the past pointing and falling. As will be discussed more fully later, van Egmond, Groen and Jongkees[102] have stressed the importance

of careful recording of the time of onset and the duration of the post-rotatory sensations. They found that the threshold of stimulation for obtaining changes in sensation was lower than that for the production of nystagmus. They, therefore, feel that a record of these sensations provides a more sensitive picture of the results of the labyrinthine stimulation than does that of nystagmus.

When a spontaneous sensation of vertigo occurs during the course of middle ear disease, it is of great significance in that it usually indicates imminent involvement of the labyrinth.

It should be noted that although the sensation of vertigo, with a definite sensation of rotation, is often due to peripheral labyrinthine stimulation, it is not pathognomonic of labyrinthine involvement, since it may also be found in association with central nervous system lesions (Alpers[2]). It is evident that other tests have to be performed before a diagnosis can be made.

SEMICIRCULAR CANAL FUNCTION TESTS. The common principle upon which the routine tests for semicircular canal function are based is the production of endolymph movement without concomitant rotation. This condition can be obtained by (1) stopping rotation, the inertia of the fluid causing a continuation of the movement, (2) calorization of the canals, producing vection currents in the fluid, and (3) mechanical pressure (positive or negative) applied to the fluid. Sometimes, a fourth method, which does not depend upon endolymph movement, is used; this is electrical stimulation of the labyrinth. In these tests, the movement of the endolymph produces reflex reactions which are similar to those produced by rotation under physiologic conditions. However, because of the absence of rotation the compensatory changes that would normally occur are translated into falling, past pointing, characteristic eye movements and sensations of rotation, without actual rotation, or vertigo.

Before describing the techniques used in the performance of these tests some points of caution need be mentioned. A careful history should be taken and a complete ear, nose and throat examination should be made. Impacted wax, foreign bodies, middle ear trauma and chronic otitis media are often the causes of patient's complaints of dizziness. The usual hearing tests should be made for both air and bone conduction. Besides pure-tone audiometry, particular attention should to be paid to speech audiometry. The presence of poor speech discrimination at higher intensities, loudness recruitment, paracusis and lowered threshold of discomfort to noise may help distinguish an end organ lesion (cochlear) from a nerve fiber lesion.

Before starting any of these tests the patient should be examined for the presence of spontaneous nystagmus, including positional nystagmus, and spontaneous past pointing. In the event that there is a spontaneous nystagmus the patient should be directed to look in the direction where there is no nystagmoid movement, or where it is at a minimum, in order that it may least interfere with the interpretation of the after-test nystagmus. It should be noted that too much significance should not be placed on small time differences of post-reaction nystagmus, because of the many variables that are usually present during the performance of these tests.

Rotation Test. This test was one of the first to be used. Although it was described earlier by others, it was Bárány[8] who systematized the test and designed a special chair for its performance. The patient is placed in a rotating chair and is usually turned

rather rapidly, about 10 times in 20 seconds, either to the right or to the left. The chair is then suddenly stopped. The character and duration of the after-nystagmus are recorded; normally it lasts about 25 seconds. Past pointing is tested as soon as the nystagmus is noted.

If the horizontal canals are to be examined the head is bent forward about 30 degrees. This places the horizontal canals in a horizontal plane at right angles to the vertical axis of rotation of the chair. When testing the vertical canals the head is placed so as to bring one pair of these canals in a horizontal plane at right angles to the vertical axis of the rotation of the chair. This is done by positioning the head forward and to one side, or backward and to one side. For example, by placing the head forward 90 degrees and rotating the chin 45 degrees toward the right, stimulation would be applied to the right anterior and the left posterior vertical canals. The results of the test are interpreted according to the laws of Flourens and Ewald. A simple way to remember what the normal reaction should be is that a labyrinth is maximally stimulated by a rotation to its side and the rapid phase of the nystagmus is to that side.

Although turning, that is, acceleration, is the physiological stimulus for the labyrinth, this test has one serious failing. That is the fact that turning stimulates both labyrinths at the same time and this makes the interpretation of the results difficult. However, when it is desired to test one pair of vertical canals, for example the left anterior and the right posterior, the turning test is valuable. It must be cautioned that in order to get correct results the head must be so placed that the pair of canals to be tested are in the same plane. If this is not done the results obtained are confusing, because the after-reactions of the different pairs of canals are not identical and it is possible to get the after-reactions of one pair of canals mixed up with those of the other pairs of canals.

The rotation test as described by Bárány[8] has been criticized by many workers for at least two reasons. First, the stimulus is too severe, and, second, it is too complex. The rapid rotation builds up strong positive angular acceleration of the endolymph and before this has finished producing its full effect on the labyrinthine receptors, the rotation is suddenly stopped, thus introducing an equally strong, negative angular acceleration in the opposite direction. Veits, in 1929, suggested that these defects could be overcome by beginning the rotation slowly and then maintaining the increased velocity at subthreshold levels. In this way the effect of the first stimulus, however slight, is certain to be over by the time the braking impulse occurs, so that the results can then be attributed solely to the braking effect. Based on these suggestions, van Egmond, Groen and Jongkees[102], in 1948, described a refined rotation test which they have termed cupulometry.

Cupulometry. Van Egmond and his co-workers[102] perform the test in the following manner. In order to exclude outside stimuli the patient is placed in a closed compartment on the turning platform. The room is darkened by using black curtains and is also soundproofed. Biconvex glasses of Frenzel[41] prevent the patient from fixing his eyes upon the surroundings. Two small lamps are used to permit inspection of the eyeballs. A subthreshold acceleration is then given until a certain angular velocity is attained. This constant velocity of rotation is continued until they feel certain that every reaction has ceased. Then the chair is abruptly brought to a standstill (in

1 to 1.5 seconds). This process is repeated using velocities of different magnitude and immediately after each stopping stimulus the duration of after-sensation and after-nystagmus is determined. The first stimulus they give is of the order of magnitude of 10 to 20 degrees per second, that is, rotating time of 18 to 36 seconds for a turn of 360°. Afterwards, the effect of smaller stimuli is tested to find the threshold stimulus, which is just sufficient to produce a sensation of turning or a nystagmus. (They have found this to be as small as 0.75 degree per second, that is, 480 seconds for a turn of 360°). After that, stronger stimuli are applied: up to 60° per second or at most 90° per second, and the reactions are recorded. The turning is then repeated at the same rate, but in the opposite direction and recordings are made of the duration of the after-sensations and after-nystagmus. They found that the duration of the deviation of the cupula, as gauged by the duration of the after-reactions, is proportional to the logarithm of the impulse and is dependent upon the threshold for angular acceleration of the individual being tested. They use a graph to describe the cupulogram. The stimuli (degrees of turning per second) are registered along the horizontal (abscissa) and the reactions (duration in seconds) along the vertical (ordinate). In normal cases a straight line is obtained. From this they conclude that in normal cases the after-reactions are dependent upon the deviation of the cupula.

In a group of 50 normal persons they found that the threshold for sensation-reaction varied from 0.75°/sec. to 5°/sec., with an average of 2.5°/sec.; for the nystagmus reaction it varied from 5°/sec. to 30°/sec., with an average of 8°/sec. Since the threshold for sensation is lower than that for nystagmus they reasoned that it could not possibly be secondary to the nystagmus and a different mode of production must exist in each case. It was found that when greater stimuli were used, shorter after-effects were obtained resulting in deviations in the curve.

They conclude that the advantages of this technique over Bárány's method are the following:

(1) An impression of the function of the semicircular canals is obtained at different points of sensitivity.

(2) The given stimulus can be regulated and is exactly known and harmless.

(3) After-sensation and after-nystagmus can be compared.

(4) When spontaneous nystagmus is present, a cupulogram for after-sensation can be made.

(5) Even very ill patients can be examined, provided they can be allowed to sit upright.

Aschan *et al.*[4], using a technique essentially similar to that of van Egmond and his co-workers[102], examined 320 adults of both sexes with negative otoneurological histories and normal audiograms. Their results and conclusions follow:

1. Statistical analysis confirmed the findings of van Egmond *et al.*, namely that, under given conditions, post-rotatory phenomena and speed are correlated, a fact illustrated graphically by the so-called cupulograms.

2. There is considerable individual variation, manifested simply as displacement up or down of the cupulogram and by the range of the threshold speeds and their means: Nystagmus-inducing speed thresholds ranged from 3.5° to 19°/sec., with a mean of 7.2°/sec. Sensation-inducing speed thresholds ranged from 1.5° to 12°/sec., with a mean of 4.5°/sec.

3. Paired observations for left and

right stimuli facilitate the detection of cupulographic "Nystagmusbereitschaft," that is, directional preponderance.

4. When rotation to the right precedes rotation to the left at all the various speeds, the nystagmus cupulogram will display a systematic directional preponderance to the left. Conversely, when the initial rotation is to the left, the resulting preponderance will be in the opposite direction.

5. A single set of observations for nystagmus duration, using contradirectional stimulation, which differ by more than 12 to 13 seconds might indicate abnormality. A consistent unidirectional difference of over 6 seconds at four to six speeds must be considered pathological.

6. The statistical results and experiences to date of "clinical cupulometry" strongly suggest that clinical usefulness of the method will spring from the nystagmus cupulogram, particularly since it provides a means of detecting directional preponderance. The sensation cupulogram does not seem equally valuable.

7. The test produced no symptoms of nausea in any of the test subjects.

Hallpike and Hood[48] constructed a new type of mechanically driven revolving chair in order to apply small regulatable stimuli. It provides angular accelerations within the range of 0.1°/sec. to 10°/sec. By means of a prismatic viewing system, which provides a stationary image of the subject's eye, direct observation of the nystagmus occurring during rotation can be noted. With this equipment they measured the duration of the after-sensations following acceleration stimuli of known magnitude and duration. They stated that their results were in striking agreement with those of van Egmond and his co-workers[102]. They also note that Steinhausen's[98] observations led him to postulate that the cupula-endolymph system was to be regarded as a heavily damped torsion pendulum, whose action could be expressed mathematically. Thus, if certain physical constants of the system, like mass, elasticity, and others, are known, it would be possible to calculate the angular displacement of the moving part (cupula) from its position of rest, in response to forces of known magnitude and duration. Also, the time required for its return to the resting position, after the displacing forces have been removed, could be calculated. In the living human subject these physical constants cannot be ascertained by direct observation, of course. However, indirect methods can be used by applying deflecting forces to the cupula of known magnitude and duration and measuring the deflection of the cupula indirectly by the duration of the after-reactions. They conclude that their experimental findings provide good support for Steinhausen's[98] concept of the cupular mechanism as a torsion pendulum.

Unquestionably, the results obtained by the use of these minimal turning tests are quite accurate and of great value. However, it should be understood that it is a relatively new, quite complicated test requiring an elaborate set-up which can be provided only by large teaching hospitals. Moreover, like all rotation tests, it has the serious drawback in that both labyrinths are stimulated simultaneously. Perhaps further clinical use of cupulometry will help to simplify the test and establish it on a firm clinical basis.

Caloric Test. Though not the first to observe the vestibular reaction after caloric stimulation, Bárány[8,9], in 1907, was the first to realize the clinical importance of this method of examination. After considerable investigation he concluded that the reaction was due to the fact that the temperature

change produced by the cold or warm water at the drum membrane is transmitted to the semicircular canals by the structures in the temporal bone. The lateral part of the horizontal canal is reached first, so that the endolymph here is either cooled or warmed and convection currents are set up in the canals that are in the vertical plane at the time of the syringing. The movement of the endolymph stimulates the ampullary receptors and vestibular reactions follow according to the laws outlined above. Calculations by Schmalz[93] concerning the conduction of heat in the petrous bone and the effect on the labyrinthine fluid helped support the theory of Bárány[7]. Bartels[12] believed that the caloric reaction was due to a direct effect on the nerves; thus, the tone of the labyrinth is increased by heat and decreased by cold. Kobrak[59] felt that the caloric response was caused by vascular reactions, the vessels in the periphery of the labyrinth being constricted by a cold stimulus and the central vessels consequently reacting with dilatation. The changes in the vessels cause a movement of the endolymph which stimulates the vestibular receptors. Borries[14,15] thought that the caloric reaction was due to a reaction by the whole labyrinth, especially the otoliths, because even when the canals were extirpated a normal caloric response could be obtained (Fujimori[42]). Brunner[21] theorized that the caloric reaction was of central, rather than peripheral, origin.

The generally accepted theory is that of Bárány[8], namely that the labyrinth is stimulated by a change of temperature and the direction of the nystagmus is dependent not only upon the temperature of the irrigating solution, but also upon the position of the patient's head at the time of the test. When the head is erect the two vertical semicircular canals, the anterior and posterior, are stimulated simultaneously, producing a nystagmus in the frontal plane, a so-called rotatory nystagmus. By positioning the head 90 degrees backward or forward, so that the horizontal semicircular canals are now in a vertical plane, caloric stimulation will then affect mainly the horizontal canals, resulting in a horizontal nystagmus. Bárány[8] further concluded that if there was no reaction to caloric stimulation the labyrinth tested was either abnormal or nonfunctioning.

In the early days, a large quantity of water well above or below body temperature was used. However, this caused severe reactions and was quite unpleasant. Experiments by Magnus, de Kleyn, and Socin[28,29] showed that even small quantities of cold water in the ear canal caused temperature changes in the lateral wall of the labyrinth. Maier and Lion[79], and later Steinhausen[98], demonstrated movements of the cupula with caloric stimulation even when the temperature of the water differed from that of the body by only one-half of a degree.

A strong stimulant is often less effective than a weaker one, particularly if the temperature of the water used for the test differs considerably from the temperature of the body. The explanation given is that when a very cold or very warm stimulus is applied and the temperature change reaches the petrous bone, the lateral part of the horizontal canal will be quickly cooled or heated, while the rest of the labyrinth is unchanged. In this way a difference in the fluid density is produced at different parts of the labyrinth. As the stimulus (for example, cold water) continues, the cooling reaches other parts of the labyrinth so that the difference in temperature between the two points is diminished,

being less than it was at the beginning. Sometimes, at the end of a long period of testing with cold water, a reverse nystagmus occurs at the end of the test. This has been explained as follows: As the cold wave proceeds, it cools the innermost parts of the labyrinth until at the end it is cooler than the external portion, so that a flow of endolymph occurs in a direction opposite to the initial flow.

According to Jonkees[54], Bárány's theory helps to explain the phenomena enumerated as follows: (1) The direction of all the vestibular reactions which result from caloric stimulation; (2) the effect of variations in the position of the head on the direction of the nystagmus; (3) the fact that long and strong caloric stimulation may inhibit the vestibular reaction (Kobrak[59], Grahe[46]); (4) the occasional reversal of the nystagmus at the end of a long caloric test; and (5) the propulsion and retropulsion caused by bilateral irrigation (Fischer and Veits[39]). In this case the effects of stimulating the two horizontal canals nullify each other, but the effects of the vertical canal stimulation are additive, so that either a propulsion or retropulsion is produced, depending upon the position of the head and the type of the stimulus, that is, whether it is hot or cold.

The phenomena which cannot as yet be explained by Bárány's theory are the following: (1) The fact that the caloric reaction can sometimes be elicited after the semicircular canals or even the entire labyrinth have been destroyed; (2) the more marked nystagmus resulting from cold stimulation as compared to warm stimulation; and (3) the fact that there is a lower threshold for nystagmus than for the sensation of dizziness, in contrast to rotatory stimulation which causes an after-sensation sooner than a nystagmus. These discrepancies may possibly be due to vascular influences and influences from the otoliths and the central nervous system. In general, however, the theory of Bárány remains the most satisfactory in explaining the phenomena provoked by the caloric test.

Wodak[109] observes that the reactions seen with the caloric test are not physiological, but pathological ones endangering the equilibrium of the person tested. Checking mechanisms, located in different places in the brain, intervene to restore the disturbed equilibrium, thus suppressing the reaction. If one or more of these mechanisms is not functioning normally due to inflammation, tumor, or the like, the reaction to the stimulus will be free of restriction, therefore exaggerated and of increased duration. However, the tonic reflexes may not all be similarly exaggerated, so that the nystagmus may be prolonged, while the deviation reaction may be normal, and *vice versa*. Such a dissociation of reflexes is of diagnostic importance.

Before the test the patient should be told what is going to be done and what possible sensations he can expect to experience. It is also wise to test first the side which is thought to be normal, lest the other side be hyperactive and the patient be frightened by a severe reaction. The ears should be examined to be sure that there is no obstruction like cerumen, a cholesteatomatous exudate or exostosis. Also, one must be certain that there are no dry perforations of the ear drum. In the event that there is a perforation cold air can be used. A device for this purpose was invented by Dundas Grant. It consists of a coiled copper tube covered with cloth mesh. By spraying ethyl chloride on the cloth the air passing through the coiled tube is cooled. By attaching one end to the compressed air outlet commonly used

for sprays, cold air can readily be obtained for the test. This method can also be used when the drum is intact. Normally, douching the ear with cold air for about 20 seconds will elicit a nystagmus lasting from 2 to 2½ minutes. If it is desirable to perform a caloric test soon after a mastoid operation, where sterility is necessary, a sterile saline or sulfonamide solution may be instilled into the open mastoid wound or external ear canal.

Position of the Head. According to Brunings[20], the stimulus, that is, the temperature and quantity of water necessary to elicit nystagmus, is different with different positions. Jongkees[55], however, could not corroborate this statement, nor could he find any great influence of position over a large range of stimulation. On the other hand, he stated that moving a subject's head during the testing variously affected the duration of the nystagmus in different patients and in the same patient at different times. He, therefore, doubts the quantitative value of a caloric test performed on a patient who is moved during the testing. Jongkees[55] feels that the best position is for the patient to lie horizontally with the head raised on a pillow at an angle of about 30 degrees. Atkinson[6] states that the head should be in such a position that the external semicircular canal is in the vertical plane with the ampulla at the highest point. This is achieved by leaning the head over to the horizontal so that one ear is above the other (the body has to lean over as well) and tilting the chin upward through 45 degrees by rotating the neck. Wodak[111] performs the caloric test with the patient sitting up, the head being in a normal upright position. McNally and Stuart[83] state that the patient may be sitting up or lying down, but the position of the head during each test should be the same. At the end of the stimulation the fluid should be decanted from the ear canal and the head placed in a predetermined position before recording the results of the test. To observe the effect upon the vertical canals, the head should be in the erect position, tilted forward 30 degrees from the horizontal. The head is then moved backwards 90 degrees so that the horizontal canals are brought into the vertical plane. (The reaction from the horizontal canals usually outlasts that of the vertical canals and is usually more marked.) Cawthorne, Fitzgerald and Hallpike[24,25] perform the test with the patient lying down so that the horizontal canals are in a vertical plane.

In 1923, Kobrak[60] advised the use of a small amount of liquid, just enough above or below body temperature to elicit a mild labyrinthine reaction, without causing nausea or vomiting. This minimal caloric test has been modified in minor respects by a number of workers.

Before describing his method, Atkinson[6] enumerates the qualifications that a valuable vestibular function test should possess, as follows: (1) It must be simple to perform. (2) It must be time saving. (3) It must test each vestibule separately. (4) It must use a minimal adequate stimulus. (5) It must be quantitative, to permit accurate comparison. (6) Its results must be capable of simple expression so as to be universally understood.

He recommends that 1 cc. of cold water be used. A 10-cc. syringe is filled with ice water and left standing in a container of ice water for several minutes. The head is leaned over to the horizontal with one ear directly above the other and the chin tilted upward 45 degrees by rotating the neck, and then 1 cc. of the ice water is instilled into the ear to be tested.

The time of instillation is noted by

stopwatch and the patient is asked to look to the side opposite the ear being tested. The time of the first flicker of nystagmus is noted and the interval between instillation and nystagmus is noted as the *time of onset*. The ear is emptied of water and the patient is tested for nystagmus, first with the head forward 30 degrees and then with the head back 60 degrees to test all canals for nystagmus and past pointing. The time at which the nystagmus ends is then noted and the duration of the nystagmus, that is the time from beginning to end, is recorded. After several minutes, the other ear is tested in the same manner. If there is no reaction after stimulation for 3 minutes, the test is immediately repeated for 3 more minutes. If there is still no reaction the labyrinth can be considered to be dead.

The results are charted as a simple fraction, the time of the onset over the time of duration in seconds. The type and quality of the reactions are also recorded. He found that in the normal labyrinth the average time of onset of nystagmus is about 30 seconds, with variations from 15 to 60 seconds. However, he considers the relationship between the time of onset and the time of duration more important. Normally, the duration is about four times as long as the onset. If the onset is 15 seconds and the duration much more than 60 seconds, the labyrinth is considered to be hypersensitive. If the time of onset approaches the time of duration, particularly if the time of onset is about 60 seconds, the function of the labyrinth is depressed. Atkinson[6] maintains that in this way a factual report can be given of the function of the vestibule and such a standardization of the cold caloric test would be of advantage for the transmission of accurate information and for easy comparison.

During the period of nystagmus, the subject can be tested for past pointing or deviation of the arms.

De Kleyn and Versteegh[30] (1927), Vogel[107] (1929) and others studied the effects of alternate warm and cold stimulation of the labyrinth. The advantage of this method of testing is that a bidirectional flow of endolymph can be produced in the semicircular canal being examined. Jongkees[55] recommends using 50 cc. of water at temperatures of 30° C. and 44° C. The subject is tested lying down with the head raised 30 degrees on a pillow. This method of testing causes no disagreeable symptoms in the patient.

Wodak[111] syringes the ears with cold water at 20° C. or warm water at 44° C. for a period of 10 seconds. This is done with the patient sitting up, the head normally erect. After the syringing, the time of appearance of nystagmus and the time of the ending of the nystagmus are recorded. After cold water syringing, the latent period is 15 to 20 seconds and the duration of nystagmus 60 to 90 seconds. When warm water is used, the latent period is longer, 20 to 25 seconds, and the duration shorter. A short latent period, under 10 seconds, is considered to be evidence of hyperexcitability; a long latent period, over 30 seconds, evidence of hypoexcitability. He warns that these findings are significant only when they are consistently so after repeated examinations.

Cawthorne, Fitzgerald and Hallpike[24,25], in 1942, described their method in which they use water 7° above and below body temperature. To reduce discrepancies due to slight changes in temperature they use relatively large quantities of water, about 16 ounces. By using thermos jugs to hold the irrigating fluid and inserting a thermometer at the nozzle the temperature of the water can be maintained more accurately. The test is

done with the patient lying down so that the horizontal canals are in the vertical plane. The time from the beginning of stimulation to the end of the nystagmus is recorded. About five minutes is allowed to elapse between successive vestibular stimulations. The vertical canals are not tested; neither is the latent period, before the onset of nystagmus, recorded. They used a schematic diagram to record the results of the hot and cold caloric tests. In this way the findings of hypersensitivity, hyposensitivity and "directional preponderance" are readily available for fairly accurate quantitative comparison.

This method of testing is more complicated and time-consuming than the simple modifications of the Kobrak tests, but is of value when more detailed knowledge of the function of a semicircular canal is desired.

Brunner[22] advises the use of bilateral calorization. In normal subjects a properly performed bilateral calorization yields no symptoms, the stimuli being of equal intensity, but mutually antagonistic. When there is involvement of one labyrinth, bilateral calorization will produce a positive result, with nystagmus directed toward the involved side. This reaction is of peripheral origin. He states that in both infratentorial and supratentorial lesions unilateral calorization with cold water usually produces reactions of hypersensitivity, more marked on the side opposite the tumor. However, by using bilateral calorization, a positive result is obtained in cases of infratentorial tumors, and a negative result in supratentorial tumors.

Fistula Test. In this test, mechanical pressure applied to the middle ear is transmitted to the vestibule and in certain conditions produces a movement of the endolymph. When the bony wall of the labyrinth has been eroded by a chronic suppurative process in the middle ear or by a cholesteatoma, a fistula is produced between the middle ear and the labyrinth, usually in the external (horizontal) semicircular canal. Since the development of the fenestration operation, in which a labyrinthine fistula is created by surgical means, this condition has become quite common. In these cases compression of the air in the ear canal and the middle ear transmits pressure to the endolymph via the exposed labyrinth. The pressure can be applied through a Siegle speculum, by means of a Politzer bulb, or simply by applying digital pressure to the opening of the ear canal. The test is positive when nystagmus and dizziness are produced.

In the absence of a fenestration operation, a positive test is of great significance, indicating imminent invasion of the labyrinth in the course of a middle ear infection or a cholesteatomatous process and requiring surgical drainage of the mastoid bone and the middle ear.

When the fistula test is negative, it means only that no nystagmus or dizziness followed the compression of air in the ear canal on that particular occasion; it must not be interpreted to mean that there is no fistula present in the labyrinth. It is possible that a dead labyrinth is present due to destruction by disease, following formation of a fistula. Such a condition could be verified by the failure of a caloric test to elicit any vestibular reactions.

In rare instances where the stapes is unusually mobile the fistula test may produce a positive reaction. However, these cases should be relatively easy to distinguish from those in which a fistula is actually present.

This test is very simple to perform, gives important information and should always be included during the

examination of a chronic ear affection.

Galvanic Test. In this test, one electrode is placed on the mastoid process and another on an indifferent part of the body. Normally, a response is obtained to a current of 2 to 7 milliamperes. The effects occur only during the make and break of the circuit. Since all the canals are stimulated by the current, the resulting reactions are due to a combination of their effects. The nystagmus is in the direction of the current, and is a mixture of horizontal and rotatory nystagmus.

Leasure[67] states that the nystagmus resulting from galvanic tests is rotatory in normal persons, regardless of the position of the head, while Northington (see Leasure[67]) stated that it is horizontal, regardless of the position of the head. Best and Taylor[13] stated that it is mixed rotatory and horizontal.

The stimulating effects of the current are not necessarily limited to the labyrinth, but may also reach the eighth nerve and its nuclei in the brain stem. Dix, Hallpike and Harrison[31] and Ingelstedt and Walander[51] reported that the galvanic test was negative in some patients who had been treated with large doses of streptomycin. They felt that this indicated a lack of reaction not only by the labyrinth, but also by the vestibular nuclei in the brain stem. The exact location of the toxic damage has not been determined.

These tests, though only qualitative at best, are of use in those cases in which it is impossible or undesirable to perform the caloric or rotation tests and it is necessary to differentiate a labyrinthine from a retrolabyrinthine lesion. Examples of such instances are greatly disabled patients and patients with atresia or marked exostosis of the ear canal or obstruction by extensive polyp formation.

Summary and Conclusion. A review of the techniques used in performing the various vestibular function tests has been given, together with a description of the anatomy and physiology upon which these tests are based.

Since so many of these tests have to be done in the doctor's office, it is essential to obtain a test which is both simple to perform and yet adequately informative. Such a one would seem to be one of the many modifications of the Kobrak caloric test. The individual examiner should choose one of these methods and use the same technique in all his patients so that the results can be comparable. There are many sources of error in these tests and it is essential that there be as few variations as possible. An accurate record should be kept both of the method and the results in each case. In those cases where it is desirable to obtain more detailed and quantitative information, one of the more elaborate and complicated tests can be performed, the particular one depending upon its availability.

It should be remembered that unless a test result is so strikingly positive as to leave no doubt whatsoever in the examiner's mind, conclusions should not be based upon a single examination. When the tests are definitely positive or definitely negative, they are of great value in ascertaining the degree of viability of a labyrinth, in differentiating between a peripheral and a central lesion and between an infratentorial and a supratentorial lesion, and in helping to diagnose a cerebellopontine angle tumor. It should be noted that they can aid in the localization of a lesion, but not in the determination of the nature of the lesion. The tests are also of help in making an early diagnosis of actual or imminent intracranial invasion in cases of acute or chronic middle ear suppuration and cholesteatoma. They serve as an aid to otologic, neurologic and neurosurgical diagnosis.

REFERENCES

(1) **Adrian, E. D.:** J. Physiol., **101,** 389, 1943. (2) **Alpers, B. J.:** Tr. Am. Acad. Ophth., **46,** 38, 1941. (3) **Arslan, K.:** Rev. Laryng., Paris, **55,** 78, 1934. (4) **Aschan, G., Nylén, C. O., Stahle, J.,** and **Wersall, R.:** Acta oto-laryng., **42,** 451, 1952. (5) **Ashcroft, D. W.,** and **Hallpike, C. S.:** J. Physiol., **81,** 23, 1934. (6) **Atkinson, M.:** A.M.A. Arch. Otolaryng., **30,** 916, 1939.

(7) **Bárány, R.:** Monatsschr. f. Ohrenh., **40,** 193, 1906. (8) Idem: Physiologie und Pathologie (Funtions-Prüfung) des Bogengang-Apparates beim Menschen. Leipzig und Wien: Franz Deuticke, 1907. (9) Idem: Monatschr. f. Ohrenh. **50,** 229, 1907. (10) Idem: Ibid., **45,** 505, 1911. (11) **Barbey, E.:** Arch. suisses de neurol. et psychiat., **50,** 345, 1943. (12) **Bartels:** in discussion on Bárány and Wittmaack; Funktionelle Prüfung des vestibular Apparates, Ber. deutsch. otol. Gesselsch., **20,** 214, 1911. (13) **Best, C. H.,** and **Taylor, N. B.:** Physiological Basis of Medical Practice, 2nd Ed. Baltimore: Williams & Wilkins Company, 1939, p. 1370. (14) **Borries, G. V. T.:** Acta oto-laryng., **4,** 8, 1922-1923. (15) Idem: Arch. f. Ohren-, Nasen- u. Kehlopf., **113,** 117, 1925. (16) **Breuer, J.:** Med. Jahrb., **4,** 72, 1874. (17) Idem: Ibid., **5,** 86, 1875. (18) Idem: Arch. f. d. ges. Physiol., **48,** 195, 1891. (19) **Brodal, A.:** Neurological Anatomy in Relation to Clinical Medicine. London and Oxford: Clarendon Press, 1948. (20) **Brunings, H.:** Ztschr. f. Ohrenh., **63,** 20, 1911. (21) **Brunner, H.,** in **Alexander, G.,** and **Marburg, O.:** Handbuch der Neurologie des Ohres. Berlin: Urban & Schwarzenberg, **1,** 239, 1921. (22) Idem: Acta oto-laryng., **42,** 487, 1952. (23) **Buys, E.,** and **Rijlant, P.:** Arch. internat. physiol., **49,** 101, 1939.

(24) **Cawthorne, T. E., Fitzgerald, G.,** and **Hallpike, C. S.:** Brain, **65,** 138, 1942. (25) Iidem: Ibid., **65,** 161, 1942. (26) **Coppée, G.,** and **Ledoux, A.:** J. Physiol., **114,** 41, 1951. (27) **Crum Brown, A.:** J. Anat. & Physiol., **8,** 327, 1874.

(28) **de Kleyn, A., Socin, C.,** and **de Burlet, H. M.:** Arch. f. d. ges. Physiol., **160,** 407, 1915. (29) **de Kleyn, A.,** and **Magnus, R.:** Arch. f. Ophth., **96,** 368, 1918. (30) **de Kleyn, A.,** and **Versteegh, C.:** J. Laryng. & Otol., **42,** 649, 1927. (31) **Dix, M. R., Hallpike, C. S.,** and **Harrison, M. S.:** Brain, **72,** 241, 1949. (32) **Dohlman, G.:** Proc. Roy. Soc. Med., **28,** 1371, 1935. (33) Idem: Acta oto-laryng., **23,** 50, 1935. (34) **Dorcus, R. M.,** and **Mowrer, O. H.:** Ann. Otol., Rhin. & Laryng., **45,** 33, 1936. (35) **Du Bois-Reymond, E.:** Untersuchungen über thierische Elektrizität, Vol. 2. Berlin: G. Reimer, 1849, p. 256. (36) **Dusser de Barenne, J. G.,** and **de Kleyn, A.:** Arch. f. Ophth., **111,** 374, 1923.

(37) **Ewald, J. R.:** Physiologische Untersuchungen über das Endorgan des Nervus Octavus. Wiesbaden: J. F. Bergmann, 1892.

(38) **Fischer, M. H.:** Ergebn. d. Physiol., **27,** 209, 1928. (39) **Fischer, M. H.,** and **Veits, C.:** Arch. f. d. ges. Physiol., **217,** 357, 1927. (40) **Fitzgerald, G.,** and **Hallpike, C. S.:** Brain, **65,** 115, 1942. (41) **Frenzel, Z.:** Hals. Nas. u. Ohrenheilk, **12,** 637, 1925. (42) **Fujimori, S.:** Klin. Wchnschr., **3,** 885, 1924.

(43) **Gerlings, P. G.:** J. Laryng. & Otol., **62,** 147, 1948. (44) **Glorig, A.,** and **Spring, S.:** Ann. Otol. Rhin. & Laryng., **59,** 146, 1950. (45) **Goltz, F.:** Arch. f. d. ges. Physiol., **3,** 172, 1870. (46) **Grahe, K.:** Beitr. z. Anat., Physiol., Path., u. Therap. d. Ohres, **17,** 251, 1921. (47) Idem: Hirn und Ohr. Leipzig: Georg Thieme, 1932.

(48) **Hallpike, C. S.,** and **Hood, J. D.:** Acta Otolaryng., **42,** 511, 1952. (49) **Hertz, H.,** and **Riskaer, N.:** A.M.A. Arch. Otolaryng., **57,** 648, 1953. (50) **Hilger, J. A.:** Tr. Am. Otol. Soc., **38,** 176, 1950.

(51) **Ingelstedt, S.,** and **Walander, A.:** Acta oto-laryng., **37,** 523, 1949.

(52) **Jones, I. H.:** Equilibrium and Vertigo. Philadelphia: J. B. Lippincott Co., 1918. (53) **Jongkees, L. B. W.:** A.M.A. Arch. Otolaryng., **48,** 402, 1948. (54) Idem: Ibid., **48,** 645, 1948. (55) Idem: Ibid., **49,** 594, 1949. (56) Idem: J. Physiol., **110,** 447, 1949. (57) Idem: Acta oto-laryng., **38,** 18, 1950. (58) **Jung, R.,** and **Tönnies, J. F.:** Klin. Wchnschr., **26,** 513, 1948.

(59) **Kobrak, F.:** Beitr. z. Anat., Physiol., Path. u. Therap. d. Ohres, **10,** 214, 1918. (60) Idem: Ibid., **19,** 321, 1923. (61) **Kreidl, A.:** Sitzunghsb. d. k. Akad. d. Wissensch. Math.-naturs. Cl., **102,** 149, 1893. (62) **Kubo, I.:** Arch. f. d. ges. Physiol., **115,** 457, 1906. (63) **Kuilman, J.:** Ztschr. f. Hals-, Nasen- u. Ohrenh., **35,** 85, 1933.

(64) **Laudenbach, J.:** Arch. f. d. ges. Physiol., **77,** 311, 1899. (**65**) **Ledoux, A.:** Proc. 4th Internat. Cong. Otolaryng., London, 1949, p. 150. (**66**) Idem: Rev. de laryng., **72,** 265, 1951. (**67**) **Leasure, J. K.:** A.M.A. Arch. Otolaryng., **35,** 766, 1942. (**68**) **Lee, F. S.:** J. Physiol., **15,** 311, 1894. (**69**) Idem: Am. J. Physiol., **1,** 128, 1898. (**70**) **Lempert, J., Meltzer, P. E., Wever, E. G., Lawrence, M.,** and **Rambo, J. H. T.:** A.M.A. Arch. Otolaryng., **55,** 134, 1952. (**71**) **Lindsay, J. R.:** Laryngoscope, **55,** 527, 1945. (**72**) Idem: A.M.A. Arch. Otolaryng., **45,** 1, 1947. (**73**) **Lorente de Nó, R.:** Ergebn. d. Physiol., **32,** 73, 1931. (**74**) **Löwenstein, O.:** Nature, **161,** 652, 1948. (**75**) **Löwenstein, O.,** and **Roberts, T. D. M.:** Ibid., **162,** 652, 1948. (**76**) **Löwenstein, O.,** and **Sand, A.:** Proc. Roy. Soc. London, s. B., **129,** 256, 1940.

(77) **Mach, E.:** Grundlinien der Lehre von den Bewegungsempfindungen, Leipzig: Wilhelm Englemann, 1875. (**78**) **Magnus, R.:** Körperstellung. Berlin: Julius Springer, 1924. (**79**) **Maier, M.,** and **Lion, H.:** Arch. f. d. ges. Physiol., **187,** 47, 1921. (**80**) **Maxwell, S. S.:** Labyrinth and Equilibrium. Philadelphia: J. B. Lippincott Co., 1923. (**81**) **McNally, W. J.,** and **Stuart, E. A.:** Tr. Am. Acad. Ophth., **46,** 33, 1941. (**82**) Iidem: War Med., **2,** 683, 1942. (**83**) Iidem: A Manual for Post Graduates in Medicine, Am. Acad. Ophth. and Otolaryng., 1953. (**84**) **McNally, W. J.,** and **Tait, J.:** Am. J. Physiol., **75,** 155, 1925. (**85**) Iidem: Quart. J. Exper. Physiol., **23,** 147, 1933.

(86) **Nylén, C. O.:** Acta oto-laryng., Suppl. 33. 1, 1939.

(87) **Ohm, J.:** Handbuch der Neurologie des Ohres. Berlin: Urban & Schwarzenberg, **1,** 1098, 1924. (**88**) Idem: in **Brunner, H.:** Handbuch der Neurologie des Ohres. Vienna: Alexander Marburg, 1924, p. 1089.

(89) **Perlman, H. B.,** and **Case, T. J.:** Laryngoscope, **49,** 127, 1939.

(90) **Quix, F. H.:** J. Laryng. and Otol., **40,** 425 and 493, 1925. (**91**) Idem: Les méthodes d'examen de l'organe vestibulaire, Paris: Vigot Frêres, 1929.

(92) **Ross, D. A.:** J. Physiol., **86,** 117, 1936.

(93) **Schmalz, G.:** Proc. Roy. Soc. Med., **25,** 1, 1931. (**94**) **Sherrington, C. S.:** The Integrative Action of the Nervous System. New York: C. Scribner's Sons, 1911. (**95**) **Spiegel, E.,** and **Sommer, I.:** Neurology of the Eye, Ear, Nose and Throat. New York: Grune & Stratton, 1944. (**96**) **Steinhausen, W.:** Arch. f. d. ges. Physiol., **217,** 747, 1927. (**97**) Idem: Ztschr. f. Hals-, Nasen-u. Ohrenh., **29,** 211, 1931. (**98**) Idem: Arch. f. d. ges. Physiol., **232,** 500, 1933.

(99) **Tait, J.,** and **McNally, W. J.:** Phil. Tr. Roy. Soc., London, s. B. 224, 1934. (**100**) **Trendelenburg, W.,** and **Kühn, A.:** Arch. f. Physiol., 1908, p. 160.

(101) **Ulrich, H.:** Arch. f. d. ges. Physiol., **235,** 545, 1934.

(102) **Van Egmond, A. A., Groen, J. J.,** and **Jongkees, L. B. W.:** J. Laryng. & Otol., **62,** 63, 1948. (**103**) Iidem: Ibid., **63,** 299, 1949. (**104**) **Van Eyck, M.:** Acta med. belg., 1951, p. 1. (**105**) **Veits, C.:** Acta oto-laryng., **13,** 94, 1929. (**106**) **Versteegh, C.:** Ibid., **11,** 393, 1927. (**107**) **Vogel, K.:** Ztschr. f. Hals-, Nasen- u. Ohrenh., **23,** 39, 1929.

(108) **Winston, J.:** A.M.A. Arch. Otolaryng., **60,** 459, 1954. (**109**) **Wodak, E.:** Ibid., **46,** 386, 1947. (**110**) Idem: Pract. otorhino-laryng., **9,** 30, 1947. (**111**) Idem: A.M.A. Arch. Otolaryng., **55,** 381, 1952. (**112**) **Woletz, F.:** Ztschr. f. Hals-, Nasen- u. Ohrenh., **30,** 524, 1932. (**113**) **Wotzilka, G.:** Ibid., **8,** 93, 1924.

DERMATOLOGY AND SYPHILOLOGY

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PIGMENTED NEVI AND MALIGNANT MELANOMA OF THE SKIN
A SURVEY OF SOME OF THE RECENT LITERATURE

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THROUGHOUT the ages of man, the ever-present mole has been the object of much concern to our ancestors, who have pondered on its life history and significance[7]. In recent years, however, some strange impetus has magnetized interest in this field, and already the concentration of investigation has indicated great promise of favorable results. To complement the constant study of histogenesis, has come information from the histopathological and histochemical investigations, and also from the embryological studies of the neural crest hypothesis of comparative zoology.

"Fundamental to any consideration of this problem is a basic understanding of the two major competitive theories of the origin of pigmented nevi and malignant melanoma. These are the epidermal and neural theories. (The older concepts, namely, the endothelial and chromatophoric, have been virtually abandoned)"[25].

The histopathological approach to histogenesis is being led by the protagonists of the neurogenic theory, Masson, and of the epidermogenic theory, Allen, who are the modern-day champions of the pioneer views of Soldan and Unna, respectively. Although the balance of opinion has swung around to support Masson, nevertheless Allen has been an indefatigable supporter of epidermogenesis[3c,67,102,113]. Even though there has been difference in interpretation, still their joint efforts have been of the utmost value. Allen, working in the Memorial Hospital, has had the benefit of extensive clinical material for his histopathological research, with the result that his practical knowledge of the histopathology of nevi and of malignant melanoma, and their transitions, is authoritative.

The histochemistry of melanogenesis has been the field of brilliant work and writing by a group of investigators which includes Fitzpatrick, Lerner, Becker, Jr., and Montgomery. Their work has been productive of important fundamental findings with regard to histogenesis, which has clarified this whole problem.

The third approach, dealing with comparative zoological and embryological studies of neural crest migration, has been led by DuShane, Rawles, Gordon, Willier and others.

These three approaches to histogenesis are of course supplemented by clinical studies, of which the most thorough and extensive have been carried out by Pack and his associates at the Memorial Hospital.

To all intents and purposes, this review will cover the material between the period of 1946[9] up to the present date.

Fitting then, as well as timely, is this review, for, in the Progress Section of this Journal, direction should be towards items of general interest. Here, as Weidman pointed out, is the common meeting place, where the general practitioner, ever faced with the need for an exact decision on the pigmented mole, the pathologist and the surgeon, all look to the dermatologist for the answer[118].

Terminology and Classification. CLASSIFICATION. The following classification, as proposed by Allen[3c], is simple and adequate for pathological use, and with some additions, the same for clinical use.

BENIGN

(*a*) Junctional Nevus
  i) Early.
  ii) Late or premalignant.

(The clinical terms, lentigo, lentigo maligna, Malignant Freckle of Hutchinson, are all grouped as variants of the junction nevus).

(*b*) Compound Nevus.

(*c*) Intradermal Nevus.

(*d*) Blue Nevus.

(The terms, Mongolian Spot and Nevus of Ota, are considered as variants of the Blue Nevus).

(*e*) Juvenile Melanoma.

MALIGNANT

(*a*) Melanocarcinoma
  i) Superficial.
  ii) Deep.

(*b*) Malignant Blue Nevus.

Junctional Nevus. During this review the shorter word, junction nevus, will be used. Other synonyms include dermo-epidermal, marginal or active[61] nevus.

The term "lentigo" is being used less and less, but amongst the older clinicians, it remains as an irreplaceable entity, whereas the younger men tend to include it along with junction nevus. Lentigo, histopathologically, shows simply, elongation of the rete pegs, with no nevus cells, and as such it is

an early junction nevus[61]. Freckle or ephelis consists of hyperpigmentation of the basal layer of the epidermis. The next stage in the development of the junction nevus, after lentigo, appears when the nevus cells remain fairly well circumscribed within the lower epidermis. The third stage is where the lower part of the epidermis is disorganized by the diffuse scattering of nevus cells therein, constituting the premalignant junction nevus of Allen[3e] or the lentigo maligna of Becker, Sr.[7h]. Becker, Sr. feels that lentigo maligna is synonymous with the Malignant Freckle of Hutchinson. The differentiation between lentigo maligna and an acquired nevus, described by Miescher, is given by Becker, Sr. as follows,

"1. The size of the macule.

2. Progressive change, not only in growth but also in regression (Changeability is characteristic of precancerous melanosis, as against the stability of a nevus).

3. The frequent grouping of several spots by apposition of new elements.

4. Chronic plasma cell inflammation and atrophy.

5. The imminent disposition to melanoma formation[3j]".

Intradermal Nevus. In this lesion the nevus cells lie in nests in the upper part of the corium, and although they appear not to have any connection with the epidermis, they almost invariably do so, if serial sections are examined. In the lower portion of the corium the cells often become spindle-shaped and resemblances to nerve structures, such as "neuroid tubes" and "lames foliacées,"[67d] are often evident. In his article, entitled "My Conception of Cellular Nevi", Masson describes carefully exactly what he means by the terms "lames foliaceés" and neuroid tubes. These specialized structures, believed to originate from schwannian cells, are not stained by hematoxylin eosin but require either the trichrome or the silver stains for their identification. This nevus has been described by Lever[61] as "resting" but since this term implies potential activity, which practically never occurs, the term used by Arnold, "mature"[5], is preferable. In this regard, however, the remainder of Arnold's suggestions as to classification seems somewhat oversimplified.

Compound Nevus. This term requires the presence of an intradermal nevus plus evidence of junctional activity. "Compound" is preferred to "combined"[105], because the latter has also been used to denote the presence of an intradermal with a blue nevus.

Blue Nevus. The relationship of the blue nevus to Mongolian Spot and the nevus of Ota will be discussed later in this review.

Juvenile Melanoma. This lesion deserves a special place in a consideration of benign pigmented lesions of the skin. It has recently been brought before the public eye by Spitz[104b]. It presumably represents a very active junction or compound nevus, or both, having a pseudo-malignant histologic appearance.

Malignant Melanoma. The use of the term, malignant melanoma, is preferred by the reviewers for two reasons: because of its worldwide usage, and in order to avoid the controversy of descriptive cell origin. The word melanoma by itself is used to connote malignant melanoma by many authors for the sake of brevity. It is also used in continental and English writing to include moles as well.

TERMINOLOGY. The Third Conference on the Biology of Normal and Atypical Pigment Cell Growth, held in New York in 1951, adopted a uniform nomenclature which will be given here. These terms were recommended for general usage. The use of the word

melanocyte, has come into vogue, but most dermatopathologists use the word chromatophore instead of macrophage.

"Melanoblast: an embryonic cell potentially capable of producing melanin.

Melanocyte: a mature melanin producing and melanin-containing cell.

Macrophage: a cell containing phagocytized melanin.

Melanophore: A pigment effector cell in lower animals"[89].

Melanoblast. This word still enjoys widespread usage, particularly on the Continent and in the United Kingdom.

Melanocyte. This cell, previously called the melanoblast, "clear" cell of Masson[67] or dendritic cell, is the melanin-producing, dopa-positive, branched cell, occurring in the basal layer of the epidermis. In the section dealing with histogenesis, evidence will be presented to show that the Langerhans cell and the Merkel-Ranvier corpuscle are probably identical with the melanocyte. In 1952, Becker, Jr., Fitzpatrick and Montgomery introduced two alternative names, the melanodendrocyte and the melanogenocyte, but these descriptive names will probably be discarded in favor of melanocyte. When stained with hematoxylin and eosin, these cells are seen as having a clear, slightly basophilic cytoplasm, and a small, deeply basophilic nucleus. With silver or gold staining techniques, the numerous long branching processes show up, giving the basal and higher layers, the character of a syncitium.

Macrophage. Not widely used, this term could perhaps be better called a melanophage. As mentioned above, the two words, melanophore and chromatophore should strictly be left to the biologists, who have a specific use for them.

HISTOGENESIS. Allen and Spitz, in 1954, state that "The issue that appears to have occupied the major share of attention of workers in the field of pigmented tumors seems to have been not that of diagnostic or prognostic clarification, but rather the matter of the epithelial as opposed to the neural genesis of these lesions"[4b].

HISTOPATHOLOGY. *Masson's Work.* The pioneer work of Soldan[102], "On the Understanding of Pigment Cells in the Neurofibromas", was confirmed and developed by Masson[67]. The title of the latter's paper in 1926, was "Pigmented Nevi, Tumours of Nervous Origin". Thus was established the neurogenic concept of nevus cell origin. In essence, this states that nevus cells may develop from two sources: the melanocytes of the basal layer of the epidermis, and the sheath of Schwann cells of cutaneous nerves. Junction nevi develop from the melanocytes alone, whereas compound and intradermal nevi arise from both the melanocytes and also the Schwannian cells. A review of certain important points of Masson's recent article will now be given[67d]. The epidermal melanocyte is always found in the basal layer of the epidermis, and the average number of these cells is constant. (cf. Szabó [Brit. Med. J., 1, 1016, 1954] who noted that while the population density of melanocytes in the human epidermis is of the order of 1,000 per mm.^{2} in the skin of the thigh and arms, it may be 2 to 4 times as great in the skin of the face and forehead.) They are the only cells that are dopa-positive in that situation. The melanocyte introduces melanin into other cells by means of a process called "cytocrinia", by means of the dendritic prolongations of the cells. The author points out that some of the melanocytes lose their dopa-oxidase and their melanin, and, becoming separated from their position in the basal layer, pass upwards through the various layers of the epidermis. These are the Langerhans cells, or "worn-out melanoblasts". The intra-

dermal nevus is described as having a dualistic origin, its superficial portion arising from melanocytes of the basal layer which migrate down into the dermis to meet Schwannian cells. Later in the maturation of this particular lesion, when the migration of melanocytes stops, the nevus becomes the intradermal type. The author emphasizes that "All the nevic cells, whatever their origin are equivalent, possessing the same properties and endowed with the same evolutive potentialities." The various characteristic forms, "the lames foliacées", "the nevic corpuscles", are described.

In Masson's previous contribution[67b] the author discussed melanogenesis with relation to silver staining and the dopa reaction. The site and morphology of the melanocytes was described and the destiny and origin of the cells discussed.

In both of these papers, Masson has rigidly stuck to his original concepts, which he feels have stood the test of time.

In 1950, in an Italian journal Masson reported his work on blue nevi and their genesis. Since this lesion is accepted as being neurogenic in origin, no further comment concerning its histogenesis will be made here[67c].

Allen and Spitz's work. Allen and Spitz, working either separately or as a team, have written a series of fine papers in recent years on this subject. Allen has remained firm in his contention that the nevus cell has an epidermal or epithelial origin, despite a gathering weight of evidence against him.

Allen, in 1949[3c], proposed to clarify the histogenesis of malignant melanoma, using the histogenesis of nevus as a stepping stone towards that goal. In this article, first the various types of nevi are described at length. In his discussion of the junction nevus, great importance is placed on the junctional or dermo-epidermal change. This is the development of clusters of altered cells in or just above the basal layer, cells which show evidence of having lost cohesion with adjacent epidermal cells. He feels that there is an observable pattern of change of epidermal cells, from the basal layer right up to the stratum granulosum and corneum as such cells alter into nevus cells. This change is analogous to the normal changes that one can observe in the shades of morphological differences from a basal cell right through to the cells of a basal cell epithelioma, and similarly from a normal prickle cell, through to the cells of the anaplastic prickle cell carcinoma. In describing the intradermal nevus, or neuronevus, the resemblance of the deeper cells to the fibroblasts or schwannian cells is mentioned, being thought perhaps due to increased stromal pressure compressing the cells into that shape. Allen states that the structures called "lames foliacées", which are similar to Wagner-Meissner corpuscles, occur in 15 to 20% of nevi in adults. These are made up of "nevus cells loosely clustered in an acidophilic bulbous spindle of fibers" and the cells themselves resemble, closely, nearby nevus cells which are not part of the corpuscle. He notes that the "lames foliacées" are usually located comparatively more deeply than the Wagner-Meissner corpuscle, and also that they are rare in the prepubertal nevus. With regard to the blue nevus the arrangement of the spindle-shaped cells into whorls or fascicles makes it resemble a neurofibroma, and the neural genesis of this lesion is accepted. Spitz[104b] has stated that "There appears to be a remarkable difference in the incidence of junctional change in the nevi of the two age groups, (that is, children and adults: Reviewer's note). This alteration was present in 98% of the children included

in this study, and is in contrast to the reports of Allen of 12% and of Montgomery and Kernohan of 25% in their studies of adults." Allen in his 1949 paper then goes on to state that there is a striking similarity between the cells of the downgrowing part of the junction nevus and those of the intradermal nevus, when associated together to form a compound nevus, confirming an earlier observation of Unna[113]. An outline of the neuralist theory is then presented in which the nevus cell is pictured as being derived from the schwannian cell, or from one of the tactile nerve-ending modifications. These include the "lames foliacées," resembling the Wagner-Meissner corpuscles of the dermis, and the Merkel-Ranvier corpuscles and the Langerhans cells of the epidermis. As such, he says, all nevi might be considered as neurofibromas, and the malignant melanoma as a neurofibrosarcoma. He then alludes to the terminological discrepancy of calling a malignant melanoma of the skin a carcinoma, whereas elsewhere in the body it would have to be called a neurofibrosarcoma. With regard to the Merkel-Ranvier corpuscle, the author feels that this is a derivative of an epidermal cell, and states that "with regard to the clear cytoplasm of these cells, as has been demonstrated in the junctional nevi and melanomas, the feature of identical hydropic vacuolization and even dopa-positivity may obtain in cells that are unequivocally epidermal, not only of the basal but also of the spinous and granular layers." Allen doubts the very existence of Langerhans cells. Next he lists six reasons for doubting that the "lames foliacées" are proliferations of the Wagner-Meissner corpuscles: 1) Intradermal nevi rarely occur at the normal sites of these corpuscles. 2) "Lames foliacées" occur at a mid-dermis level, much lower than the corpuscles. 3) Nevus cells within a "lames foliacées" appear to be identical with those not associated with the structure. 4) "Lames foliacées" are rare in prepubertal nevi. 5) "Lames foliacées" may be "purposeless, haphazard condensations of dermal collagen about nevus cells." 6) If nerve endings are the source of nevi, why do they seldom give rise to nevi, other than on the skin and in the eyes?

The second important paper, this one by Allen and Spitz, in 1953[4], will be reviewed only as far as information is given, which is additional to that in the 1949 paper. That their views have not changed is stated firmly right at the start of the paper, with "In accordance with this concept, the junctional nevi, the intradermal nevi, the juvenile melanomas and the melanocarcinomas of both skin and mucous membranes are of epithelial origin rather than neural." A little further on, "In this current study, we might add, we have elected to omit further discussion on the histogenesis of these lesions for the time being, except to state that nothing we have observed in this material, or in the literature, has in any degree repudiated the validity of the concepts previously outlined."

It would be wise to make careful note of certain histopathological characteristics of the "active" or precancerous junction nevus: 1) "The general features of nuclear anaplasia such as hyperchromatism, increase in nuclear or nucleolar size, irregular nuclear vacuolization, and mitotic figures. 2) Subepithelial inflammatory reaction consisting preponderantly of lymphocytes. 3) Cytoplasmic vacuolization and fine melanin pigmentation reaching to the uppermost layers, that is, to the stratum granulosum and the stratum corneum."

In their most recent article, Allen

and Spitz, in 1954[4b], cover much of the material contained in their previous articles and it will suffice here to review some of the highlights. Explanation of the radioresistance of malignant melanoma is sought in the comparison with the similar situation of spindle-cell epidermoid carcinoma, whereas other types of epidermoid carcinoma are much more radiosensitive. The loss of prickles in the metastases of melanocarcinomas is considered to be compatible with the assumed neoplastic-like properties of such cells, in which their differentiation is altered away from their original potentialties. The coexistence of melanocarcinoma with xeroderma pigmentosum, reported as being 3%, is very much higher than one could statistically predict, and this is taken to infer indications of the epidermal origin of malignant melanomas. A series of questions are then listed which query the validity of the neurogenic theory, and since these present a challenge to some other authority, no comment will be offered, but we look forward to their answers. Allen and Spitz then discuss the migration of neural crest cells, which will be covered a little later in this review. With regard to Masson's views on "cytocrinia," and the presence of a constant number of melanocytes in the basal layer, the authors are in disagreement. They feel that the number of melanocytes in the basal layer is not constant, but that it varies with race, irradiation and other conditions. They also feel that the supranuclear position of melanin suggests manufacture rather than transfer. Again these melanin granules tend to be uniform in size, whereas in phagocytes, such is not the case. Concerning the hyperpigmentation sometimes seen in scar tissue, they feel that the regenerated epithelium forms its own melanocytes. In discussing the nature of the dendrites of epidermal melanocytes, certain features distinguishing these from true neural dendrites are considered, such as the absence of an axone and also the silver-staining properties. They also ask what has happened to the dendrites of the superficial or junctional component of the intradermal nevus.

The two papers by Spitz[104a,104b], since they do not deal particularly with histogenesis, will be discussed later in this review under the clinical aspects.

Other Authors. Becker, Jr., Fitzpatrick, and Montgomery, in 1952[8], made certain very pertinent observations concerning the histogenesis of nevi. With the gold impregnation technique, used by Gairns[42], Medawar and Billingham[11,12b] and with separation of the epidermis from the dermis, the authors were able to confirm the previous observations of Medawar and Billingham that there are nonpigmented melanocytes in the epidermis. An insight into the origin of the Langerhans cell was also gained when it was realized that it is the melanocyte, the same cell as those in the basal layer. Previously being thought to be high up in the epidermis, now actually known to be in the basal layer, this discrepancy was nicely demonstrated and shown, as apparently misplaced, by tissue distortion produced by the acid used in the gold impregnation process. This difficulty was overcome by using camera-lucida reconstructions of the epidermal folds, and schematic drawings to correctly place the epidermo-dermal junction in proper reference to the cells concerned. With regard to another enigma, the views of Pinkus[87] and Masson[67] were confirmed when evidence of mitotic division of melanocytes was observed after suitable ultraviolet irradiation. Other observations concerning the constant number of melanocytes in the basal layer, tyrosinase activity, production of melanin

and its release will be discussed in the section on histochemistry. That this is a very important contribution to this problem is certain and reference will be made to a statement made by Montgomery in the discussion following the reading of this paper[8]; "I am sorry that neither Dr. Samuel Peck nor Dr. S. W. Becker, Sr., are present, because they in the past have held opposite views concerning melanogenesis, and I, along with Dr. Peck, have been opposed to Masson's concept of a neuroepithelial origin of the clear and dendritic cells, whereas Dr. Becker, Sr., has supported this concept. It remained for Dr. Fitzpatrick and Dr. Becker, Jr., working in my laboratory, to convince me that the basal cells of the epidermis do not form pigment and that only the so-called dendritic cells form melanin pigment. The clear cells of Masson (cellules claires) are equivalent to the pigment-forming dendritic cells and do not arise from the basal cells of the epidermis as I, with others, formerly maintained. I am, therefore, going to have to change what I have said in the book with Ormsby, "Diseases of the Skin," in regard to the histology and histogenesis of pigmentation. Masson has recently referred to the cell of Langerhans, which is best seen with gold preparations, as a dead cell (Cancer, 4, 9, 1951). Dr. Becker, Jr., however, has clearly shown that gold impregnations of the skin resulted in wrinkling of the epidermis, and consequently serial sections revealed that the so-called Langerhans cell is not high up in the epidermis but is actually a dendritic cell lying at the epidermal-dermal junction." True to his word, Montgomery in the new edition of his book[78] has carried out a drastic reversal of his previously held position.

The contributions of Montgomery to our knowledge of nevi have always been sound and illuminating, and since this happens to be a favorite field of his, they have also been numerous. His paper with Kernohan, in 1940[73], has been extensively discussed in Beerman's review of 1946[9]. However, it is mentioned again because this study was a landmark. His contributions on blue nevus[31,72,114] will be considered when the clinical aspects of that nevus are taken up. Two other papers[71a,71c] will be referred to under the treatment of nevi. His most recent publication, with Stegmaier[105], in 1953, is an important piece of work. In this series, 100 pigmented nevi were excised from children who had been selected at random, their results, therefore, reflecting normal histopathological variation. Of the 95 nevi that were included, the other 5 having been rejected, evidence of junctional activity was present in all. Only one case showed any mitotic figures. Cell structure was uniform and most of the cells were small, a point of some differential value. Forty-seven of the nevi were classified as junctional in type, and 34 as combined. In the latter the nevus cell nests in the corium did not penetrate the linear band of connective tissue in the corium, but instead caused the skin surface to bulge upwards because of the pressure of the cell population. Superficial pigmentation was noted to be an attribute. Although non-medullated nerve fibers were seen, no "neuroid tubes" or "lames foliacées" were detected. Masson, however, states that such configurations are only found in the nevi of older people[67d]. Many of the combined nevi showed points of origin from hair follicle walls. The majority of the lesions removed from the hands and feet were junctional in type. Inflammatory infiltration was present, but was minimal in 93 out of the 95 nevi. No blue nevi turned up in this series.

Another prolific author, who has been champion of the neurogenic

theory, and whose clinical studies of nevi have been most important, is S. William Becker, Sr. In limiting the coverage of his work to the 1946 period, the number of papers is still great. "Melanin Pigmentation Throughout the Ages"[7] demonstrates his versatility and includes a study of the pigmentation of whale skin, as well as a review of pigmentary processes in certain lower zoological phyla.

In 1949 his paper, "Diagnosis and Treatment of Pigmented Nevi,"[7c] is designed to point out some of the pitfalls of therapy. In this paper, he followed an old classification of Miescher and Albertini, in which nevi were grouped as follows: A) Epidermal segregation with groups and cords of cells. B) An infiltrative growth exclusively intradermal. C) Neurofibromatous structure resembling von Recklinghausen's neurofibroma. These groups could be combined to illustrate composite features. Becker varied this classification a little as follows: A) Lesions in which nevus cells are still definitely attached to, or actually integrated into, the corium. B) Lesions in which no nevus cells are definitely attached to the epidermis but in which they are present in the dermis. C) Nerve type nevus of Masson, some portions of which resemble neurofibroma. The accuracy of clinical versus histopathological diagnosis of pigmented nevi was tabulated, and this will be covered later in this review.

In 1951[7d] and 1954[7f], two general reviews were published, the material contained in which will be mentioned elsewhere in this paper.

Becker, Sr., in his contribution to the Third Conference of Pigment Cell Growth[7b] described the normal cutaneous melanocytes occurring in normal skin, in separated epidermis, and in embryonic skin. His own classification of nevi follows, which has already been listed. The author mentions the difficulty of accepting the theory that nevi develop from melanocytes, which penetrated as far as the dermo-epidermal junction in early life, then later returned to the dermis to form nevi. The existence of non-pigmented nevi in which no pigment can be shown, even by Bizzozero's silver method, is recognized, and most show nevus cells only in the deepest part of the dermis. Becker mentions the figure of 25% as being the percentage of malignant melanomas that have a definite antecedant history of origin in a pigmented nevus. He is, of course, theoretically quite correct that only serial sections would determine this figure accurately. With regard to usage of junction nevus as a descriptive term, Becker remains in disagreement, preferring to retain the more established terms of "quiescent nevus," "active nevus" and "lentigo maligna." The variability of cell differentiation in malignant melanoma renders its histological classification difficult and of indifferent usefulness. However, malignant melanoma, in its earlier stages, can be seen originating from lentigo maligna, which Becker, Sr., properly calls malignant melanoma *in situ*, and from a nevus. In the latter instance he states, concerning the origin, "Whether from normal melanoblasts or from nevus cells cannot be determined, but pathologic theory maintains that malignant cells arise *de novo* and not from benignly neoplastic cells. It has been my impression that clear cells are often better developed, or perhaps even present in greater numbers over superficial nevi, which may account for the more frequent occurrence of melanoma in such pigmented nevi." Certain of his other remarks are of interest. "The nevus which is most likely to become malignant is the smooth brown one. The blue-black nevus, which is alleged to be the dangerous variety, is already malignant."

With regard to the essentials of the histopathological picture of malignant melanoma, the key is anaplasia. Although not a feature of the early lesion, its presence may be suggestive of prognostic significance. However, other authors have stated that the histopathological picture cannot be correlated with prognosis. Other features, such as the depth of the pigment, degree of cutaneous infiltration, and number of mitotic figures, were not of much assistance.

Becker, Sr.'s paper, in 1954[7g], lists certain figures concerning the origin of malignant melanomas in preexisting moles. These will be taken up in the section of histopathological correlations.

A second paper[7h], in 1954, is a particularly useful contribution, because in it, Becker attempts to clarify the status of a junction nevus as far as its activity is concerned. He states that junction nevus includes three distinct lesions, which are described as, 1) The quiescent, smooth, pigmented nevus. 2) The active, smooth, pigmented nevus. 3) Lentigo maligna. In his first group, this lesion is found especially on the lower extremities, genitalia and particularly on the feet. In it there is a minimal degree of anaplasia, little epidermal disorganization and minimal inflammation and pigmentation. In the second, the lesion is enlarging or becoming darker, or both. Microscopically there is more evidence of pigmentation and inflammation with some tumor cells in the stratum corneum. These two stages can be said to correspond to Allen and Spitz's[4b] early junction nevus. The third stage shows slow but steady enlargement, in which the nevus cells show definite anaplasia, with epidermal disorganization, and with inflammation in the corium. This is the premalignant junction nevus of Allen[3c] and of Lever[61]. Becker, Sr., likes to call this lentigo maligna and to regard it as identical with Hutchinson's Malignant Freckle. However, Klauder and Beerman[57] are of the opinion that the malignant freckle runs a more benign course in older people.

Cawley and Curtis[19] have written a timely paper entitled "Lentigo Senilis" in which, as an introduction, they have given a careful description of the difference between lentigines and freckles. They list the most important distinctions, compiled from their work and that of Brown[15]. "Ephelides first appear later in life (6 to 8 years), are located on the exposed surfaces most commonly, increase in number after exposure to sunlight, are a light brown or chamois color, contain no dopa-positive cells, never develop into cancer, do not follow infections and are relatively transitory. In contrast, lentigines appear most commonly for the first time in the third year of life, occur on all parts of the body, do not increase in number after exposure to sunlight, are usually dark brown, contain dopa-positive cells as part of a microscopic architecture, which differs considerably from that of ephelides, sometimes undergoes malignant changes, are often more numerous after infections and persist for years." Cawley and Curtis go on to describe lentigo senilis or "liver spots," those lesions that appear after the fourth or fifth decade, and increase slowly, both in size and number. Of irregular shape, they may grow to a size of 1 cm. in diameter, may vary from a few to many, and in color, from a light to dark brown. Occurring in 25 to 30% of people over 50 years of age, they are probably part of the aging process, and since they never become malignant, should be recognized as such.

Berkheiser and Rappaport, in 1952[10], published the results of a small series of cases, 7 junction, 30 compound nevi

and 12 malignant melanomas. They felt that their views tended to support Masson's theory of nevus cell origin from epidermal melanocytes, and from sheath of Schwann cells. They pointed out the fact that elements suggestive of nerve structures were more common in older nevi.

Lund and Stobbe[64] discussed certain factors of age and anatomic location of nevi. They found four features of nevi that were influenced by age: 1) Junctional activity. 2) Mitotic figures. 3) Size (or total cellularity). 4) Differentiation to fibrillar or other nerve-like forms. The natural history of the pigmented nevus was traced out, with the final or mature form containing fibrils and fusiform cells. Contrary to Masson's ideas, however, they did not feel that this indicated a possible source of nevus cells. This report has been widely referred to in the literature.

The development of epidermal pigmentation in the Negro fetus has been described by Zimmermann and Cornbleet[126] in 1948. It has long been known that such pigmentation normally continued for 2 months after the birth of the child. Dendritic melanocytes appeared in the third month of intrauterine life and at that time probably only contained a premelanin. During the fourth and subsequent months, the dopa-oxidase reaction became positive and the melanocytes could be identified by ordinary silver nitrate preparations. The ameboid movement, first noticed in living frog skin by Ehrmann in 1885, was presumed to be the method by which they reached the epidermis. Later the increase in secondary branching of the dendritic processes became evident, as they surrounded the ordinary epithelial cells with their tenuous processes. In the fifth month, brown pigment granules appeared in the melanocytes and their processes, and the authors felt that there was an active transfer of melanin to ordinary epithelial cells at this time. This latter process became more apparent in the 6th and 7th months, as did the formation of supranuclear caps, well known in adult epidermal preparations.

Raven[91] who has contributed widely to the English and Continental literature on this subject puts forth some of his views in "Pigment Cell Growth." He mentions the incidence of melanomas in the skin of animals, where it is found almost exclusively in the skin, and feels that there may well be genetic factors concerned. Of moles as precursors of malignant melanoma, he mentions a rate of 30% (95 out of 316 cases, collected from the literature). In a description of the morphology of the melanocyte, a graphic picture is drawn suggesting that the motility and mobility of those cells are an expression of their aggressive properties of malignancy. The malignant cells are described as being "not adherent and tend to separate from the main tumor, singly or in groups," thus being able, as individual cells, to pass filtering obstacles, and being, in addition, capable of reproduction in a far-distant, highly specialized location. The divergence of pigmentation in the primary and secondary sites may be a feature of the "high metastasizing potential possessed by the malignant melanoma."

In recent years, there have been three articles by English authors dealing with pigmented epidermal tumors of the skin. In 1948, Stewart and Bonser published a study of 57 such cases, which included 21 squamous papillomas (syn. seborrheic verruca), 2 benign calcified epitheliomas, 28 basal cell carcinomas and 6 squamous carcinomas. They feel that such tumors behave very much like their non-melanin forming epidermal counterparts. With regard to the origin of the

pigment, the authors believe that the tumor cells themselves formed the melanin, mentioning a previously considered fact that there was no evidence of an intact surface epithelium being a requirement, nor were the deeper portions of the tumors necessarily less pigmented than the more superficial[106].

Lennox, in 1950, wrote on "Pigment Patterns in Epithelial Tumors of the Skin"[58], based on his material of 311 biopsies, examined by a modification of Masson's silver method. In his series, 67% of squamous papillomata, which numbered 51 cases, and 37% of basal carcinomata, which included 124 cases, were pigmented. Benign calcifying epitheliomata, 3 cases, and squamous carcinomata, 51 cases, all were non-pigmented. The author noticed characteristic pigment patterns, which corresponded to the histological picture. The presence of melanocytes, along the dermo-epidermal junction, tended to indicate the benignity of the process, and failure to find pigment is associated with portending malignant change. In his studies of basal cell epithelioma, he found melanocytes scattered at random in the highly pigmented islands, where the pigment was found in both the epithelial cells and the melanocytes. Lennox suggests that, when this work is confirmed, the following conclusions seem justifiable. "a) The presence of a definite pigmented basal layer or of basement-membrane-orientated melanoblasts is strong evidence against malignancy in a squamous papilloma. In small tangentially cut biopsies in which invasiveness cannot be assessed, this may be of considerable value. Localized malignancy elsewhere in the tumor cannot, of course, be excluded by this means.

b) An invasive tumour which contains melanin is almost certainly a rodent ulcer and not a squamous carcinoma.

c) The generalisation that no pigmented epithelial tumour of the skin has ever been known to metastasize may be of value in the prognosis.

d) Though irrelevant to the main theme, it may be worth noting that one should never have any real difficulty in distinguishing between a malignant melanoma and a pigmented epithelial tumour. The appearance of fully differentiated melanoblasts, with delicate branching processes, lying among tumour cells of an entirely different type and without intermediate forms, is quite unlike that of the melanomata, which only exceptionally show good dendritic forms. Further, the anaplastic squamous carcinomata, which alone are likely, on general morphological grounds, to be confused with melanomata, are never pigmented. Diagnosis of the amelanotic melanoma is a different matter: occasionally, however, melanin can be demonstrated in an apparently pigment-free melanoma by the silver reaction."

Lennox goes on to discuss the origin of melanin in these pigmented epithelial tumors and states that the presence of melanocytes in the tumor does not mean that they alone, and not the epidermal cells, can produce melanin. However, as we have already seen, evidence[8] points to the fact that the melanocyte is the only cell which can produce melanin, which confirms Lennox's view.

The difficult clinical and histopathological differentiation between sclerosing angioma (histiocytoma) and malignant melanoma was brought out by Ewing and Powell in 1951[34]. With regard to the frequency of this lesion, they point out that Rentiers and Montgomery[93], in 1949, were able to report a series of 95 cases, and that Allen[3] in his study of 8000 specimens of skin received by the Army Institute of Pathology during World War II

included 426 tumors with this diagnosis. After a discussion of the clinical features of this lesion, the authors decide "that there is no certain way clinically of distinguishing between the two" and even that the pathological diagnosis is difficult. In order to assist histopathological exclusion, the use of the silver reticulin stain in demonstrating blood vessel structures, and the identification of the pigment, by either Masson's silver stain or by bleaching with acid potassium permanganate, is of considerable value.

HISTOCHEMISTRY. The pioneer in the field of histochemistry in its relation to the histogenesis of pigmented and malignant melanoma was Bruno Bloch, whose early work in 1927[13] has been ably described by Lerner and Fitzpatrick[59] and which will be quoted herewith. "Bloch, a Swiss dermatologist, stimulated by this hypothesis (enzymatic oxidation to form melanin, Reviewer's note) attempted to prove it by experimental methods. His approach was directed by two clinical observations. First, melanin pigmentation is a prominent feature of Addison's disease, a disorder resulting from hypofunction of the adrenal glands. The possibility arose that there might be some relationship, albeit a pardoxical one, between the increased pigmentation and the metabolism of epinephrine-like substances. Second, in cases of metastatic melanoma with melanuria, the urine contained significant amounts of catechol derivatives. These facts suggested to Bloch a chemical similarity between the precursor of melanin and the compounds epinephrine and catechol. He therefore selected a naturally occurring amino acid, 3,4 dihydroxyphenylalanine (which he abbreviated as DOPA, using the initial letters of its German name, di-oxyphenylalanine) as the substrate for histochemical studies.

Bloch immersed frozen sections of pigmented human skin in a 1:1000 solution of dopa buffered to pH 7.3 to 7.4. He noted that after 24 hours at room temperature melanin granules were deposited in the cytoplasm of cells located in the basal layer of the epidermis. These specialized cells, which Bloch called melanoblasts, are located at the epidermo-dermal junction and were considered by Bloch to be the natural site of melanin formation. The intensity of the response, moreover, corresponded to the known capacity of the skin to form melanin. Melanin deposition was most intense in the areas of the skin capable of heavy pigmentation, such as the basal layer of the epidermis, the germinal layer and cells of the hair matrix, and the cells of pigmented nevi. Melanin deposition did not occur in albino skin and in the skin of patients with vitiligo, a skin disease characterized by localized areas of complete loss of melanin pigment. Bloch therefore concluded that the "dopa reaction" was a reliable indication of the capacity of the cells to form pigment." To quote further from a paper by Fitzpatrick, Becker, Jr., Lerner and Montgomery[37], 1950, "The investigators found that incubation of the skin with compounds other than dopa, for example, tyrosine and epinephrine, did not result in formation of melanin in the melanoblasts. Therefore, Bloch concluded that the melanoblasts in human skin contained a specific "dopa oxidase" which could catalyze the oxidation of dopa only to melanin."

"Several years later, Raper[90] showed that dopa was the first product formed in the enzymatic oxidation of tyrosine to melanin by tyrosinase of plant and insect sources. He also demonstrated that plant and insect tyrosinase could catalyze the oxidation of dopa, as well as of tyrosine, to melanin; that is, plant

and insect tyrosinase possesses tyrosinase and dopa-oxidase activities."

"In the past 8 years, it has been demonstrated that extracts from melanomas of mice, horses and human beings display both tyrosinase and dopa-oxidase activities. Furthermore it has been shown that, under certain conditions, a true distinction cannot be made between tyrosinase and dopa-oxidase activities in mammalian tissues. It was recommended that the term tyrosinase be used for this enzymatic activity, instead of the terms tyrosinase and dopa-oxidase."

In the report that follows, the authors demonstrate the presence of tyrosinase activity in human skin. This was shown by the deposition of melanin granules in the cytoplasm and dendrites of melanocytes after incubation of human skin with tyrosine solutions. It is important to add that the above experiments were positive only when intact, living skin had been previously irradiated with ultraviolet light, and the mechanism for this action is not known. It was concluded that human epidermal tyrosinase ordinarily exists in a partially inhibited state and is released only after some stimulus, such as ultraviolet light.

Flesch and Rothman[40], in 1948, felt that this state was due to the presence of sulfhydryl groups, which inhibit tyrosinase by combining with copper, a metal essential for the enzymic activity.

Fitzpatrick[36], in 1952, discusses the tyrosinase system further: "It is possible that as we ascend phylogenetically from plants to man a control is placed over the activity of tyrosinase and the enzyme is active only during periods of physiological production of melanin, and only when the melanogenocytes (the term preferred by Fitzpatrick, in 1952, Reviewer's note) are exposed to activating factors, such as radiant energy, hormones, and so forth. The controlled rate of activity is lost when the pigment cell becomes malignant. In this case melanin production is limited only by the availability of the substrate."

Fitzpatrick was able to show in his biochemical and histochemical studies that the non-irradiated human skin, pigmented moles, ephelides, lentigines and verrucae seniles possessed an inhibited tyrosinase system, whereas in irradiated human skin and in malignant melanoma, there was an uninhibited or active tyrosinase system:

"Further investigation may clarify the mechanism of the activation of the tyrosinase system and the reasons why tyrosinase in the normal melanocyte is present in the inhibited state. The chemical identification of the naturally occurring inhibitory factor or factors in the normal human pigment cell and nevus cell may serve as a pattern for the development and localization of specific inhibitors of tyrosinase in the malignant melanoma cell. As these inhibitory factors become clearer so will the likelihood increase of finding a rational chemotherapeutic approach to the treatment of one of the most devastating and sinister of malignant lesions." Finally, the author states that the tyrosinase system might be a means of distinguishing an amelanotic melanoma from other neoplasms.

The preceding presentations on histochemistry in relation to histogenesis have indicated that: 1) the melanocyte forms melanin, 2) that normal human skin has an inhibited tyrosinase system. It will now be pointed out that, 3) the melanocyte is the only cell in which tyrosinase activity could be demonstrated by histochemical means, 4) that the melanocyte is the only cell in the epidermis which can produce melanin. Becker, Jr., Fitzpatrick and Montgomery[8] have performed certain experiments with Thorium X stimula-

tion to observe its effect on the tyrosinase system. With a careful histopathological follow-up, they found no evidence of enzyme activity in the basal cells but only in the melanocytes. With regard to melanin formation, a special technique was used in the preparation of slides for its observation. This is carefully described and includes a separation of the epidermis from the dermis. Sections for microscopic study were taken from the bisection plane so that they were from anatomically identical areas. Three days after stimulation, there was evidence of increased melanin in the melanocytes and melanin appeared in the stratum corneum on the seventh day. By the eleventh day the stratum corneum contained a great deal of pigment but the melanocytes were not yet filled, as shown by the fact that vertical sections did not show nuclear caps on the basal layer. By the fourteenth to eighteenth day, maximal pigmentation was attained, and at this time there were no pigmented basal cells. In the basal cell layer the melanin granules were observed to lie entirely within the melanocytes, the nuclear caps actually being granules at the tips of dendrites. In the prickle cell layer, the melanin lay in the dendrites. The authors observed that, although the numbers of melanocytes is constant in unirradiated skin, there was an increase after Thorium X stimulation in their numbers.

Lerner, Shizume and Fitzpatrick, in 1953[60], produced a preliminary report which shows for the first time that Melanocyte-Stimulating Hormone (MSH) by injection can cause darkening of both frog and human skin. It is believed that MSH is a separate hormone although present preparations contain small amounts of ACTH, vasopressin and oxytocin. This hormone is largely responsible (nor-adrenaline, adrenaline, hydrocortisone and progesterone playing a role) for the pigmentation of Addison's disease and pregnancy.

Shizume, Lerner and Fitzpatrick[101] have recently described a method of *in vitro* quantitative bioassay for MSH.

NEURAL CREST HYPOTHESIS. Harrison, in the "Biology of the Melanomas," in 1948[47b], described the neural crest in an interesting manner. "For a long time, the study of pigment development was held back by our lack of knowledge of the source of the pigment cells. They seemed just to appear in definitive position without giving evidence of their place of origin. Not even the germ layer whence they came was known until well along into the present century. There were several lucky guesses but nothing more substantial. Then, about 12 years ago, came the experimental proof that pigment cells in the amphibia arise from the neural crest, and several years later this was similarly shown for birds and again more recently for the mouse. At once, many puzzles in the developmental behavior of pigment cells began to clear up. The neural crest was known to be a very versatile embryonic rudiment, giving rise not only to certain ganglia and the neurilemma of peripheral nerves, but also to the cartilaginous visceral skeleton, and contributing at the same time to the mesenchyme and the meninges, particularly the pia-arachnoid. It is characterized by its mobility and capacity to spread all over the body from its line of origin around the rim of the neural plate, where at first it lies between the prospective central nervous system and the general ectodermal coverings of the body. In their movements, the cells are guided by the surrounding tissues, although the tendency to aggregate or to distribute themselves diffusely is of genetic origin. It was only through the discovery of such facts that the pe-

culiar behavior of pigment cells in normal development and after experimental intervention could be understood."

In his new book, "The Neural Crest"[52] Hörstadius devotes a 20-page chapter to pigment cells, in which the embryological studies in lower forms of life are reviewed (Lennox[58] also gives a readable summary of this work). Hörstadius mentions that Borcea, in 1909[14], and Harrison, in 1910[47a], were the first to consider that the neural crest might be the origin of pigment cells. Their work was done on amphibians. It was not until 1934, however, that DuShane[33] proved conclusively that this was the case in amphibians, when he removed bilaterally the trunk neural crest. That such observations included the epidermal melanoblasts, as well as of other regions, was brought out by DuShane, in 1935, and by others later. Hörstadius goes on to say that "the pathways of migrating melanoblasts are not known, as the cells at this stage have not yet formed pigment and are impossible to distinguish from other mesenchyme cells." He also refers to the excellent reviews by DuShane[33b] and by Rawles[92]. The work of other leaders in this field, such as Twitty and Willier is mentioned, and an excellent list of references is given. Lennox[58] adds, "It seems improbable that a process established with such consistency in the rest of the vertebrate phylum, occurring at a stable phase of embryonic development when species differences are minimal, has been fundamentally altered during the evolution of the mammal. Even in mammals it will require some very strong factual evidence to shake the neural-crest hypothesis now."

Pigment Spread. It seems appropriate to mention the phenomenon of pigment spread at this point. Two English workers, Medawar and Billingham[11a,b,12a,b,70] have done a great deal of work on this subject. The phenomenon has been described by them as follows, "When a spotted black and white guinea pig is born, the areas of black skin bearing black hairs are incisively distinct from the areas of white skin bearing white hairs; but as it grows up, the superficial epidermis at the boundaries of the white areas is slowly, evenly and progressively encroached upon by pigment. The white hairs are unaffected." A similar process may be observed for experimental purposes by grafting black skin into white areas. The authors speak of this as an "infective cellular transformation" in which as Lorincz puts it[63], there is "an infective spread of mitochondrial self-duplicating pigment granules into colorless melanocytes in white-skin areas via the 'cytocrine' activity of the melanocytes." In 1947, Haxthausen[48] performed transplantation experiments on cases of vitiligo and congenital lentigo. In these cases the process of pigment spread did not occur, but instead the transplant tended to adopt the characteristics of the surrounding skin. Similar results were obtained by Spencer and Tolmach in 1952[103].

PIGMENTED NEVI. CLINICAL FEATURES OF PIGMENTED NEVI. (Reviewer's Note—Much of the material regarding the clinical features of pigmented nevi has been taken from the unpublished data of Dr. B. Shaffer, including Tables 1 to 6[99].)

JUNCTION NEVUS. It has been said[104b] that pigmented nevi may be present at birth, however it is felt that such an event is unusual. Observation of many children indicates that the incidence of pigmented nevi gradually increases up until the age of puberty. Nevi often develop in crops or showers, and in certain individuals these showers continue to make their appearance from time to time until very late in puberty

or even sometimes into early adult life. When a new shower of these pigmented lesions is first observed, they are found to fall, as a rule, into a rather characteristic morphologic type. They are usually flat and macular. While on superficial examination they may appear to be sharply demarcated from the normal skin, a more careful scrutiny, especially with a hand lens, reveals a somewhat fuzzy and slightly indistinct border. The density of the pigment appears to vary within the lesion itself so that frequently they will have a stippled or a speckled appearance[44]. The amount and degree of total pigmentation also varies considerably. Some of the lesions are rather light, yellowish-brown and others are a deep brownish-black. Most of the lesions in a single shower, however, have about the same shade of color.

TABLE 1.—EVOLUTION OF MELANOCYTES IN MAN[99]

IN UTERO The melanocytes migrate from the neural crest to the following,

1. Epidermo-dermal junction.
2. Uveal tract.
3. Occasional foci in the corium.
4. Pia mater about medulla.
5. Mucosal surfaces.

POST UTERO

1. At epidermo-dermal junction, the melanocyte forms:
   a) Normal skin pigment.
   b) Latent foci, which may develop into:
      i. Pigmented nevus.
      ii. Malignant melanoma.
2. Uveal tract melanocytes produce:
   a) Normal pigment.
   b) Malignant melanoma.
3. Occasional foci in corium produce:
   a) Mongolian Spots.
   b) Blue nevi.
   c) Malignant melanoma rarely.
4. Foci in pia mater produce pigmented meninges.
5. Activation of foci in mucosal surfaces produces:
   a) Occasional pigmentation.
   b) Occasional malignant melanoma.

TABLE 2.—CLINICAL FEATURES OF JUNCTION NEVUS[99]

1. Appears usually early in life, frequently in crops.
2. Flat or only slightly elevated.
3. Border fuzzy.
4. Pigment speckled or mottled.
5. Evolves into compound and into intradermal types.
6. On the palms, soles and genitals, apt to persist as junction nevi throughout life.
7. Has little or no malignant potentiality until puberty.
8. Only a very few junction nevi persisting after puberty ever become malignant.

COMPOUND NEVUS. In older age groups, the lesions mentioned above become less common, and other types of pigmented lesions take their place. The trunk and the extremities particularly are the sites of pigmented lesions that are elevated and distinctly verrucoid in appearance, characterized by digitate, polypoid or warty formations. These again are, on superficial examination, found to be sharply marginated, but a closer inspection discloses, at the periphery of such lesions, a thin or very narrow macular halo or ring, circumscribing the verrucoid formation at its base. In various age groups and sometimes even in the same individual, all transitional stages between the typical, early, flat, macular, speckled nevus, and the well-developed, verrucoid, pigmented nevus may be observed. Some lesions of this type take on a keratotic character, so that the surface of the lesion is elevated, roughened and capped by an adherent, greyish scale. At still other times, many of the primary macular lesions appear to have evolved into elevated, flabby, sessile or saccular, pedunculated tags. Here again, one can often see a narrow, nonelevated, pigmented halo about the base of these lesions and, in addition, one can sometimes observe various transitional forms between the macular

nevus and the fully developed sessile or pedunculated nevus, from which the macular halo has finally disappeared. These changes, of a sessile, fibrotic or pedunculated type, are most apt to appear on the trunk as compared to the verrucoid and keratotic changes, which seem to be more common on the extremities.

TABLE 3.—CLINICAL FEATURES OF COMPOUND NEVUS[99]

1. Of many years duration, usually prepubertal or older.
2. Almost invariably elevated but often with a macular ring or halo about periphery.
3. Clinical variants:
   a. Verrucoid.
   b. Keratotic.
   c. Sessile or pedunculated.

INTRADERMAL NEVUS. On the face and to a lesser extent on the scalp, the flat, macular nevus seems rather rapidly to turn into a smooth, elevated, fleshy nodule, which may vary from several millimeters to one centimeter in diameter. These lesions appear to mature at an earlier age than do the other lesions described above and are often found on the faces of adolescents. They become more common as age progresses, and continue to appear, and sometimes to grow, even into old age. While some of these lesions are pigmented, sometimes deeply so, many are very light or contain no coloring at all. A surprisingly large number of these lesions are associated with the development of coarse hairs, resulting in combinations of pigmented and hairy nevi. These latter lesions reach their full development most commonly at puberty. Verrucoid, keratotic or flabby saccular lesions which have no halo, especially those that are partially or completely pedunculated, are also apt to be of the intradermal variety.

JUVENILE MELANOMA. "Occasionally, however, there occur in children pigmented lesions morphologically identical with the malignant melanomas of adults. These are clinically smooth, elevated, brownish red and hairless." This description by Spitz[104a] introduces the juvenile melanoma, a lesion, which, although rare, should be recognized because of its prognostic implications. The latter consist of the fact that such lesions are clinically benign and do not metastasize. Hormonal factors and that strange stepping stone, the age of puberty, apparently play a role in this condition, as well as in nevi and malignant melanoma as a whole, but, as yet, there is not an inkling of the mechanism.

TABLE 4.—CLINICAL FEATURES OF INTRADERMAL NEVUS[99]

1. Develops from a pre-existing compound nevus.
2. Of many years duration, usually late puberty or older.
3. Almost invariably elevated, with no macular ring or halo.
4. Clinical variants:
   a. Verrucoid.
   b. Keratotic.
   c. Smooth, elevated, with or without hairs.
   d. Flabby, fibrotic, sessile or pedunculated nodules or tags.

A definitive histopathological diagnosis of juvenile melanoma can be made by an expert, and Allen and Spitz[4a] list the following features: "1) The relative superficiality of the essential landmarks of the lesion. 2) The two elements of a compound nevus, junctional and intradermal. 3) Edema and telangiectasia of the cutis just below the epidermis. 4) The tendency for single cells or compact nest of spherical or spindled cells to be segregated sharply from adjacent ones. 5) The occurrence of large cells with abundant, usually uni-

formly basophilic, myogenous-appearing cytoplasm. 6) The superficially located, characteristic giant cells, those with the single large nucleus, as well as the multinucleated ones resembling the pattern either of the giant cells of measles or of Touton giant cells, with a complete or incomplete peripheral rim of small nuclei. 7) The generally abrupt transition between the acantholytic, loose junctional cells and the still intact, adjacent epidermis. 8) The relative sparsity of the pigmentation so that, in association with the superficial dermal edema and telangiectasis, most of the juvenile melanomas clinically appear purplish red rather than dark brown. In addition to this fairly distinctive coloration, the juvenile melanomas tend to be hairless, larger, and more elevated than the usual nevus of childhood."

TABLE 5.—CLINICAL FEATURES OF JUVENILE MELANOMA[99]

1. Usually before puberty.
2. Rapid growth.
3. Usually elevated.
4. As a rule, not much pigment, often reddish or violaceous in color.
5. Clinical variants:
   a. Smooth elevated.
   b. Verrucoid.
   c. Keratotic.

It is important to realize that the occasional juvenile melanoma may persist into adult life.

BLUE NEVUS. An authoritative paper on blue nevus has recently been published by Dorsey and Montgomery[31] and it replaces Montgomery's previous contribution, with Kahler in 1939[72]. Much of the material contained here has been taken from the recent paper.

Incidence. Montgomery, in 1944[71c], indicated that he had seen 100 cases of blue nevus. Ten years later[31], his experience has increased to include 500 cases, 200 of which are included in the present study.

Clinical Findings. Two types are described, the common, discrete type, occasionally multiple, and the larger type, usually cellular, which is uncommon. The average size of the former is from 2 to 10 mm. in diameter. Not all blue nevi are present at birth. The color is most commonly blue-black and is due to melanin. However, according to the location and depth, they can be blue, or steel-blue, down to gray, brown and even yellow. Slightly more than half were found on or near the dorsa of the hands and feet, none on the palms and only one on the sole.

Histopathology. A detailed description of the histopathological picture, which is diagnostic, is given. Irregular masses of large, spindle-shaped, dendritic cells are located in the lower two-thirds of the cutis with an overlying area of normal cutis. The cells are several times larger than the melanocytes of the basal layer of the epidermis and are dopa-positive in early life. With regard to origin, Dorsey and Montgomery seem hesitant to accept Masson's theory of origin from the sheath of Schwann of peripheral nerves. Two reasons given were that transitional forms had not been seen, and also that nerve fibrils could not be demonstrated in close relation.

Mongolian Spot. This lesion which appears in every child of the Mongolian race, in the sacral region, and in white children on rare occasions, is present at birth and later fades away.[31,56]. The cells, which are identical with the blue nevus cells and are dopa-positive, are sparsely distributed in the dermis. Although commonly seen in the sacral region, they can occur elsewhere, especially on the extremities.

The case reported by Upshaw, Ghormley and Montgomery in 1947 as an extensive blue nevus which per-

sisted and infiltrated deeply down to muscle, is apparently now considered to have been a Mongolian Spot[114].

Nevus of Ota. Described by Ota, in 1939[56], this lesion is described by Dorsey and Montgomery[31] as being a Mongolian Spot involving the side of the face and the eye. The nevus penetrates deeply into the deeper structures of the face and eye, including the sclera, retro-orbital fat and even the periosteum. The authors quite rightly suggest that the recent case reports, one by Pariser and Beerman[86], describing an "Extensive Blue Patchlike Pigmentation," and by Cole, Hubler and Lund, "Persistent, Aberrent Mongolian Spots" (3 of their 4 cases)[22], belong to the diagnosis of nevus of Ota. Similarly the more recent case reports of Hyman[54] and Wigley[119] and Carleton and Biggs[16] might be considered variants. Dorsey and Montgomery summarize this view when they state "It would appear that the blue nevus, Mongolian Spot and the nevus of Ota are closely related and possibly represent different stages of the same process." It is hoped by these reviewers that the unwieldy, descriptive name of this condition, nevus fusco-caeruleus ophthalmo-maxillaris of Ota, will suffer its deserved fate.

TABLE 6.—MELANOCYTIC LESIONS OF THE SKIN[99]

1. Melanocytes at epidermo-dermal junction: life history of the pigmented nevus.
   a. Junction nevus.
   b. Compound nevus.
   c. Intradermal nevus.
2. Melanocytes in the corium.
   a. Mongolian Spot.
   b. Blue nevus.
   c. Nevus of Ota.
3. Malignant melanoma develops from:
   a. Junction nevus.
   b. Compound nevus.
   c. Juvenile melanoma.
   d. Blue nevus.
   e. Nevus of Ota.

Malignant Change. a. Blue nevus. The difficulty in classifying the cellular type of blue nevus, which has minute metastasizing ability, with the true malignant blue nevus has confused the reported incidence of malignant change. It would appear from Dorsey and Montgomery's summary that a maximum of 13 cases of malignant blue nevus have been reported.

b. Nevus of Ota. The same authors report the first 2 cases ever described of malignant degeneration in the nevus of Ota[31].

DIFFERENTIAL DIAGNOSIS PIGMENTED NEVI. The reader is referred to the equivalent section in the discussion of malignant melanoma.

TABLE 7.

Authors	*Total Number of Melanomas*	*Percentage with Pre-existing Mole*
Wright[124]	94	49
Daland and Holmes[26]	128	44.6
Pack[81]	862	50
Ackermann[2]	75	61
Driver and McVicar[32]	60	80
Totals	1219	56.9

HISTOPATHOLOGICAL: CORRELATION AND FEATURES. CORRELATION. *Origin of Melanoma in Pre-existing Mole.* The following table has been taken from Cunningham[25], with certain changes.

Which nevus becomes malignant? The answer to this question can be given unequivocally: the junction nevus and, by virtue of its junctional component, the compound nevus. Other pigmented nevi only rarely do so. Allen[4b] states "in our opinion, the junctional nevus or the junctional component of the compound nevus is the forerunner

of all malignant melanomas of the skin and mucous membranes, the rare malignant blue nevus excepted."

Accuracy of Diagnosis of Nevi. Becker, Sr.[7c], points out that, in a series of 710 specimens submitted to his laboratory with the clinical diagnosis of pigmented nevus, that diagnosis was found to be correct in 80% of cases. On the other hand, in a series of 649 lesions on which the histopathological diagnosis of pigmented nevus was made, the clinical diagnosis was correct in 87% of cases. Swerdlow's figures[108] are 61% and 74% respectively for another large series. The latter attributes the discrepancy to the relative clinical experience of the examiners in the two series.

Differential Diagnosis. There are several informative papers in recent years which are of great value in reviewing those lesions most apt to be mistaken for pigmented nevi. These include those by Becker, Sr.[7c,7e,7g] dealing with "Diagnosis and Treatment of Pigmented Nevi," "Pitfalls in the Diagnosis and Treatment of Melanoma" and "Seborrheic Keratosis and Verruca." Others are, Beerman[9], "Tumors of the Skin," Caro and Szymanski[17], "Seborrheic and Senile Keratoses," Montgomery[71c], "Benign and Malignant Moles" and Sachs, MacKee and Sachs[97], "Keratoses, Seborrheic and Senile."

Reference to the tables in the articles by Becker, Sr.[7c], and by Swerdlow[108] will show the lists of the lesions confused for nevi. The one lesion most frequently mistaken for a pigmented nevus was the seborrheic keratosis. Other lesions to be excluded include squamous-cell (hard) papilloma; basal cell epithelioma, especially the pigmented variety; hemangiomas and verrucae vulgaris.

FEATURES. *Evolution.* If one examines a section of normal skin, one can frequently see at the epidermodermal junction, a number of round cells, with clear cytoplasm containing a round, dark-staining nucleus. These are the clear cells or melanocytes, as they appear in the ordinary hematoxylin and eosin stain. The pigmented nevus, of the flat speckled type, that so commonly develops in showers in young people, when examined histologically shows a marked increase in the numbers of these melanocytes which are grouped into clusters directly beneath the basal layer, where they are called nevus cells. These clusters are connected to the basal layer in such a fashion that they appear to be "dropping off" and this so-called junctional activity characterizes the junction nevus. On examining elevated nevi, and particularly those of the verrucoid, keratotic or sessile varieties, the incidence of junctional activity diminishes, so that such foci can be found only occasionally across the epidermal base. In such lesions large aggregated strands and bundles of nevus cells are found in the corium, and as a rule, there is a definite band of fibrous tissue between the nevus cluster and the basal layer. This type of nevus is the compound or intermediate nevus and it represents a transitional stage in the life history of the pigmented nevus. In a fully mature nevus, all junctional activity has ceased and a definite band of fibrous tissue, sometimes exceedingly fine, narrow and tenuous, but at other times broad and easily detected, completely separates the nevus cell nests in the corium from the epidermis. This lesion is now the intradermal, cellular or mature nevus.

Allen[4b] lists certain histopathological features for the intradermal type which will be summarized here: 1) No junctional activity. 2) Giant cells present. 3) Never encapsulated. 4) Rare prior to puberty.

Junctional Activity. It is believed, as

has been mentioned, that only those nevi which show junctional activity have malignant potentiality. Consequently the astute clinician should make every effort to identify such lesions by their clinical appearance. This is a difficult job because most writers feel that there is little correlation between the clinical appearance of the junction nevus and histological evidence of junctional activity. Tables 2 to 5 inclusive summarize the clinical highlights of the differences in the various types of nevi and should assist in diagnosing the junction nevus. Allen and Spitz list certain features of the junction nevus which should aid in their histological diagnosis. These are as follows: a) the quiescent junction nevus: 1) a loss of cohesion of cells beginning with the basal cells and extending upwards. 2) Associated vacuolization and loss of prickles. 3) Scattered and increased melanin pigmentation, b) the active or precancerous junction nevus: 1) Nuclear anaplasia. 2) Subepithelial inflammatory reaction of lymphocytes. 3) Cytoplasmic vacuolization. 4) Fine melanin pigmentation up to stratum corneum[4].

Shaffer[99] has pointed out that it is not so much the age of the patient that determines the degree of junctional activity, as it is the age of the lesion, and the rate at which it is maturing. Heretofore authors have emphasized that junctional activity was a reflection largely of the age of the patient. However, fully mature nevi have been found in very young babies. This makes one believe that, firstly, when nevi appear very early in infancy, they have more time to mature when the patient is still young, and secondly, they undergo a very rapid evolution in correspondence with the rapid development of all tissues of the body. It is a fallacy, therefore, to depend solely on the age of the individual in order to predict the degree of junctional activity. Rather one should consider: 1) the age at which the nevus first appeared; 2) the duration of the lesion; 3) the current age of the individual; 4) the appearance of the lesion itself.

Significance of Age. In this review, the question of age has come up on repeated occasions, and apart from the remarks made in the preceding paragraph, other considerations will be taken up now. Pratt[88] has stated that pigmented nevi were rarely present at birth. He found only 24 pigmented nevi in his series of 879 white infants. This is at variance with the previously expressed opinion[71c,104b]. However, nevi can first appear at an early age, and when they do so, they are almost always junctional in type. Spitz has made a much-quoted remark that 98% of nevi in childhood showed junctional change versus only 12% in adults[104b].

There are certain histological features of nevi in childhood, which have been listed by Allen and Spitz[4a] as, 1) Junctional change in 98%. 2) Intradermal component more cellular than those nevi of later years. 3) "Lames foliacées" are absent. 4) Less fibrosis is present. 5) Giant cells are more common. 6) Mitotic figures are rare.

By 1948, Spitz[104b] had collected 13 cases of juvenile melanoma, which is an indication of the rarity of that lesion. It is stated that two-thirds of these can be definitively diagnosed histologically by an expert. Even when the small percentage of such are seen in adult life, certain remnants of their structure permits recognition. In a small percentage of malignant melanoma (5.9%) according to Allen and Spitz[4a] residual characteristic structure of juvenile melanoma remains.

Malignant melanoma in children is a rare disease, and those cases which have been reported will be reviewed in the section on that disease.

(To be Concluded in the May, 1955 issue)

PROCEEDINGS OF
The Physiological Society of Philadelphia
SESSION OF DECEMBER 21, 1954

INFORMAL SEMINAR ON SOME PROBLEMS INVOLVING MEASUREMENT OF CARDIAC OUTPUT

Introductory Remarks. LYSLE H. PETERSON, M.D. (Departments of Physiology, Anesthesia and Surgery, University of Pennsylvania). Accurate measurement of blood flow is as important to the development of cardiovascular physiology as that of urine flow is to renal physiology, or as that of gas flow is to respiratory physiology. Unfortunately most blood vessels are inaccessible, the flow within them is unstable, and blood is nonhomogeneous. Many methods have been used to measure blood flow in isolated vessels, but only two principles have received widespread, serious application to the measurement of total blood flow or cardiac output. These are the dilution and clearance principles. The first serious attempt to establish a measure of cardiac output in man appears to have been about 1910. At that time two schools of thought developed. They are now known as the "low" and the "high" schools. The low school developed in Copenhagen where Krogh *et al.*, utilizing a method of N_2O equilibration, reported normal cardiac output to be about 4 to 5 L/min. In England, Douglas *et al.*, utilizing a somewhat similar O_2 method, reported values of 5 to 8 L/min. In this country Henderson developed an ethyl iodide method which yielded values compatible with the English school. Later Grollman, using acetylene, and Starr, using a modified ethyl iodide method, developed what appears to be a "medium low" school. In any event it took 30 years to establish some idea about the magnitude of "normal" cardiac output. Yet, most agree that normal cardiac output is a variable depending, among other things, upon physiologic needs, that is, the heart is the servant and not the master. The indirect Fick has become almost the standard of reference in output methodology. However, the search continues for a method to measure it more easily, accurately, and rapidly. Indicator dilution methods have been revived and revised. Many workers are attempting to deduce stroke volume from arterial pulse pressure and the ballistocardiogram. Each of the speakers tonight is a leader in the field of cardiac output methodology. Each treads the line between a desire to obtain physiological information and a desire to evaluate his data with respect to the limitations of his methods; a feat which requires considerable wisdom.

Calculation of Cardiac Output from Analysis of Aortic Pressure Pulses During Very Rapid Venous Bleeding. DAVID F. OPDYKE, M.D. and MARY E. ZANETTI. (Merck Institute for Therapeutic Research, Rahway, N. J.) Very rapid venous bleeding at a constant rate (200 to 500 cc./minute) in dogs results in a rectilinear decrease in arterial blood pressure (pressure plotted against bleeding volume in cc./kg.) which is independent of changes in heart rate and vasomotion initiated by

the stimulus of bleeding. The decline in cardiac output is thought to parallel the decline in arterial pressure. Cardiac stroke indices and outputs were calculated from the phasic aortic pressure pulses by the Hamilton-Remington method at frequent intervals (2 to 3 seconds) during the rapid venous bleeding. Plots of the decline in the calculated cardiac output failed to correlate with the observed decline in arterial pressure in the intact dogs, but good correspondence was obtained from high-spinal-transected and vagotomized dogs. In the presence of a slow and constant heart rate and in the absence of reflex vasomotor activity the arterial pressure and calculated cardiac output change in parallel fashion. This seemingly precludes the use of the Hamilton-Remington cardiac output method when cardiac output is changing rapidly in the intact dog.

Instantaneous Pulmonary Capillary Blood Flow. ARTHUR B. DUBOIS, M.D. and GRANT DEJ. LEE, M.D. (Dept. Physiology and Pharmacology, University of Pennsylvania Graduate School of Medicine). Measurement of instantaneous pulmonary capillary blood flow by a new method consisting of rate of absorption of N_2O by a subject in an airtight body plethysmograph (DuBois and Lee) yielded pulsatile flow curves in normal individuals at rest and immediately after exercise (20 knee bends). The latter showed an increase in mean cardiac output consisting of increased stroke output of the right ventricle or tachycardia, or both. Upon comparison of the curves at rest and during exercise it seems as if the factors to be considered are: Force of contraction of the right ventricle, elasticity of the pulmonary arterial tree, pulmonary arteriolar resistance to blood flow, and inertia of the blood. By electrocardiographic timing, one can determine that the first factor operates during increasing flow, and that the other three determine the downstroke. The downstroke of the pulse wave was steeper after exercise than it was at rest, so that the excess blood in the pulmonary arterial tree has just enough time to get out of the way of the succeeding stroke from the right ventricle. There are two possible explanations for this change with exercise: the first is that the pulmonary arterial tree is less compliant, and the second is that the pulmonary arteriolar resistance decreases with exercise. Differentiation between these two possibilities ultimately rests on simultanously measuring instantaneous pulmonary capillary blood flow and pulmonary arterial pressure.

Cardiac Output by Cuvette Oximeter. E. M. GREISHEIMER, PH.D., M.D., D. ELLIS, A.B., and G. STEWART, B.S. (Depts. of Physiology and Medical Physics, Temple University, School of Medicine). The concentration of dye in whole blood can be recorded continuously by means of the cuvette oximeter. Light of constant intensity is passed through the cuvette oximeter into two photoelectric cells. One cell, the infrared, indicates total hemoglobin concentration. The other, the red, indicates the concentration of the dye, if the hemoglobin is saturated with oxygen. The electric output is recorded by a galvanometer of the d'Arsonval type. The circuit is so arranged that either the output of the infrared cell alone may be recorded or the red and infrared currents may be bucked against each other and only the differential recorded. The dye concentration is calculated from the deflection of the galvanometer beam, by means of a calibration curve. The final concentrations of dye in the blood used for calibration covers a range from 11.5 to 92.3 mg./L. With the weakest dye the actual deflection of the galvanometer

beam is 6.08, and with the strongest 11.11 cm.; with no dye present the beam's position is 4.62 cm.

The actual amount of dye injected is determined by weight; in a large number of experiments the range covered is 8 to 23 mg./m² in individual dye curves. The amount of dye injected does not determine the cardiac index, as shown by the following examples. In one dog the index was 8.57, after the injection of 11.4 mg./m² of dye and in another, the index was 1.49 after the injection of 17.5 mg./m² of dye. The depth of anesthesia is not the determining factor of cardiac index; the cyclopropane concentration in the arterial blood of the above two dogs was 21.1 and 21.4 mg. per 100 cc. respectively.

We have found that the cardiac index increases most under thiopental sodium, next under ether anesthesia. Under cyclopropane, the cardiac index remains quite steady during six successive dye curves.

When the experiment is begun under cyclopropane, and then ether added, the cardiac index increases.

When the experiment is begun under thiopental sodium, and then cyclopropane added, the cardiac index does not increase as under thiopental sodium alone.

Tests of the Ballistocardiogram as a Method for Measuring Cardiac Output. ISAAC STARR, M.D. (Dept. Therapeutic Research, University of Pennsylvania). Experiments in which systole was simulated by injections of blood into the aorta and pulmonary artery of cadavers at necropsy afford a method of testing the various methods of estimating stroke volume from the amplitude of ballistocardiograms (Am. J. Physiol., **127**, 1, 1939). We have analyzed data from 51 simulated systoles in 5 cadavers in which the known stroke volume could be compared with that estimated from the ballistocardiogram taken when systole was simulated. The correlation between estimates of stroke volume from the wave altitude formula, $SV=7\sqrt{(31+2J)}AC^{3/2}$ and true stroke volume was 0.69, the standard deviation about the regression 10.6 cc. The correlation of the estimates from the old wave area formula, $SV=33\sqrt{(21+J)}A\sqrt{C}$ and the true values was 0.73 and $\sigma_T=9.7$ cc. That of Tanner's formula (J. Clin. Invest., **28**, 567, 1949) $SV=100\sqrt{(2I+J)}\sqrt{C}$ and the true values was 0.73, while $\sigma_T=10$ cc. Therefore, all three formulae provide rough estimates of the relative values for cardiac stroke volume and no more was ever claimed for them. However, the Tanner estimate yields values much too high, perhaps because its constant was adjusted in the assumption that the average stroke volume of subjects lying relaxed and at rest on the ballistocardiograph was similar to that of subjects breathing through a mouthpiece, and with catheter and arterial needle in place, during a Fick estimation. Multiple regression equations relating amplitude of ballistocardiogram, size of subject and the true stroke value were calculated by Dr. A. Schild. In the most interesting of these $SV=27+42\sqrt{(2I+J)}\sqrt{C}-24$ B.S.A. (where I and J are the areas of the I and J waves of the ballistocardiogram in mm.sec. when 10 mm. = 280 gm. body surface area is in m², and C, the duration of the cardiac cycle in sec.) In our data 2/3 of these estimates are within 8 cc. of the true value.

BOOK REVIEWS AND NOTICES

NEW BOOKS

Air Pollution and Community Health. By CLARENCE A. MILLS, M.D., PH.D., Prof. of Experimental Medicine, University of Cincinnati. Pp. 180. Boston: The Christopher Publishing House, 1954. Price, $2.75.

THIS little volume is dedicated to those victims who have died in poison smogs, and to an earnest appeal for eliminating this major hazard to community health which completely overshadows the purely "nuisance" aspects of dirty air arising from worldwide industrialization and urban air pollution. As pointed out by the author, the inhalation of smokes and smogs may result not only in irritation of the upper respiratory tract but constitute important factors in the etiology of bronchitis, asthma, pulmonary fibrosis, pneumonia, tuberculosis, cancer and congestive heart failure as well. Indeed the author is of the opinion that community rights to clean air should be protected by law while industrial physicians and hygienists continue their efforts in assisting industries to develop better methods for the prevention and control of air pollution. J. K.

Streptococcal Infections. Edited by MACLYN MCCARTY, Hospital of the Rockefeller Institute for Medical Research. Pp. 218; 27 ills. New York: Columbia University Press, 1954. Price, $5.00.

THIS small volume stems from a symposium held in February, 1953, under the auspices of the Microbiology Section of the New York Academy of Medicine. Recognized authorities were invited to read papers which summarize the present state of knowledge in each of the areas represented by the special interests of the individual investigators. The basic biology of Group A streptococci is covered rather completely in five presentations, as are also certain phases of the immunology and pathogenesis of streptococcal infections. E. S.

Endemic Goiter. The Adaptation of Man to Iodine Deficiency. By JOHN B. STANBURY, M.D., GORDON L. BROWNELL, PH.D., DOUGLAS S. RIGGS, M.D., HECTOR PERINETTI, M.D., JUAN ITOIZ, PH.D., AND ENRIQUE B. DEL CASTILLO, M.D. Pp. 290; 52 ills. Cambridge, Mass.: Harvard University Press, 1954. Price, $4.00.

IT has been known for some time that goiter is endemic in the province of Mendoza, Argentina. Approximately 27,000 school girls between the ages of 6 and 16 were examined and 18.4% of them were found to have visible goiters of which one-third were distinctly nodular. This monograph constitutes a report of the studies performed in an effort to investigate the pathogenesis and pathologic physiology of these goiters. Employing newer methods of investigation including I-131 and PBI determinations, it was established that these glands were "iodine hungry." The thyroid hyperplasia was considered to be an effort on the part of the gland to compensate for a deficiency in the dietary iodine intake. Although the serum protein-bound iodine was generally within the normal range, the avidity of the thyroid gland for iodine was shown to be increased as manifested by the high thyroidal I-131 uptake.

This monograph is written in a lucid, easily understandable style and will prove to be of great interest to internists as well as to workers in the field. W. P.

Diencephalon, Autonomic and Extrapyramidal Functions. By WALTER RUDOLF HESS, M.D., Professor of Physiology, Emeritus, University of Zurich, Switzerland. Pp. 79; 33 ills. New York: Grune & Stratton, 1954. Price, $4.00.

THIS is an interesting and important book by a qualified investigator who was selected for the Nobel Award in Physiology and Medicine in 1949. This work is very useful because it represents a source in English for a large number of German publications by the author. An interesting technique involving localized stimulation and destruction in unrestrained animals is presented. The integration of autonomic functions is stressed. M. O.

The Six Schizophrenias. Reaction Patterns in Children and Adults. By SAMUEL J. BECK, PH.D. Pp. 238. New York: American Orthopsychiatric Assn., Inc., 1954. Price, $5.00.

THE Six Schizophrenias is the result of a 5-year research program by a multidisciplining team of psychologists, social workers and psychiatrists in which their findings are correlated by the Q method. This is a very interesting, though highly technical monograph on a new approach to the problem of schizophrenia. This monograph is primarily for researchers who are acquainted with the Rorschach technique. A. H.

Das Fibrinogen. By DOZ. DR. MED. HABIL. FRIEDRICH-HORST SCHULZ. Pp. 143; 90 ills. Stuttgart: Georg Thieme Verlag, 1953 (Intercontinental Book Corporation, New York, U. S. Agents). Price, DM 17.60.

THIS is a comprehensive monograph on fibrinogen. The author discusses the chemistry and physical chemistry of fibrin and fibrinogen; the various methods for their determination; the

physiological and pathological variations of fibrinogen; its biologic significance; and its site of formation. The volume is well-illustrated, and is recommended to anyone desiring a basic review on this substance. It is written in German.

C. Z.

First International Conference of National Committees on Vital and Health Statistics. WHO Technical Report Series No. 85. Pp. 27. Geneva: World Health Organization, 1954. Price, $.25.

Fifty Years of Medicine. By Lord Horder, G.C.V.O., M.D., F.R.C.P. Pp. 70. New York: Philosophical Library, Inc., 1954. Price, $2.50.

A great clinician and teacher reviews briefly his own years in the medical profession and the advances which he has seen made and helped to make, and ventures a few prophesies. First presented in the three Harben Lectures delivered in December, 1952, at the Royal Institute of Public Health and Hygiene, the material has been expanded somewhat under the headings "Birth of Scientific Medicine," "Medicine Enlarges Its Boundaries," and "The Present and the Future." The excellence of this little volume leaves one with a single regret: its brevity.

R. K.

Of Publishing Scientific Papers. By George E. Burch, M.D., F.A.C.P. Pp. 40; 18 ills. New York: Grune & Stratton, 1954. Price, $2.75.

A delightful and instructive booklet that should be read by all prospective writers of scientific papers, editors of scientific journals, publishers and advertisers. The good which it could be hoped thus to accomplish rapidly lessens in the order named. The illustrations are superb.

R. K.

A Methodological, Psychiatric and Statistical Study of a Large Swedish Rural Population. By Tage Larsson and Torsten Sjögren. Pp. 250; 12 ills. Copenhagen: Ejnar Munksgaard, 1954. Price, 25 Swedish Crowns.

This is a study aimed at making a statistical and genetic analysis of psychosis and low grade oligophrenia over a long period and in a circumscribed area. The study has been carried out by the period method. In 1951, the percentage of hospitalized schizophrenia was 22%. There was no significant increase in first cousin marriages in psychotics but there was a greater frequency of consanguineous marriages in the families of oligophrenics than in the general population. As in most countries the need for more beds for the feebleminded in Sweden is urgent: the urbanization and industrialization making the problem more pressing over and above an apparent increase in the number of cases diagnosed: an increase of 33% over the periods 1941-1950.

Space prohibits the presentation of many other interesting statistics. The book has extensive tables and references.

O. E.

La Voix. By Edouard Garde, Speech Consultant, l'Hopitál Boucicaut, Laryngologist, Maîtrise de la Radiodiffusion francaise. Pp. 128; 15 ills. Paris: Presses Universitaires de France, 1954. Price, not given.

This paper back volume presents a concise but comprehensive review of the known facts concerning the anatomy and physiology of the larynx and discusses in detail the cerebral centers and the pathways concerned in speech. In addition to the detailed description of laryngoscopic, stroboscopic and tomographic examinations, there is an excellent tonal classification of the voice.

H. S..

Chemotherapy of Infections. By H. O. J. Collier, Ph.D., M.I. Biol., Chief Pharmacologist, Allen and Hansbury, Ltd. Pp. 248; 53 ills. New York: John Wiley & Sons, Inc., 1954. Price, $4.00.

This is a well-written and practical little volume reviewing the fundamental principles involved in infections and their control by chemotherapeutic means and the mode of application of the several antibiotics. There are also special chapters on the chemotherapy of tuberculosis and leprosy, certain tropical diseases and the malarias. The terminology follows the British usage, which, however, does not present much difficulty.

R. K.

Why We Became Doctors. Edited by Noah D. Fabricant, M.D. Pp. 182. New York: Grune & Stratton, 1954. Price, $3.75.

Every physician would naturally find some interest in knowing why others chose the profession which he himself has entered. Therefore, this book holds the attention of medical readers from first to last. There are presented the reasons for their choice by 50 physicians, 9 of them in chapters written especially for this book, the others having stated their reasons in previous publications. The names of a few will vouch for the interest of what they all say: Havelock Ellis, Somerset Maugham, Sigmund Freud, Marion Sims, W. T. Grenfell, Albert Schweitzer, A. J. Cronin, Oliver Wendell Holmes, George Crile and Hans Zinsser. The non-medical reader, however, should not fall into the error of assuming that these fifty are a representative sample of the profession and should not draw any generalizing conclusions (a more accurate title would have been "Why They Became Doctors").

R. K.

Parkinsonism and Its Treatment. Edited by Lewis J. Doshay, M.D., M.A., Ph.D., Dept. of Neurology, College of Physicians and Surgeons, Columbia University. Pp.

152; 18 ills. Philadelphia: J. B. Lippincott Co., 1954. Price, $3.00.

THIS little book, reasonably priced, and easy to carry with one for reading at odd free moments, is heartily recommended by the reviewer. It is written for "medical students and practicing physicians," and meets that aim admirably. To the man who has to care for these patients, the book offers much.

To be sure there are one or two points with which some might take issue but, with such disease as this, that is to be expected. That there are some differences of opinion is called attention to in the text. The list of authors is a distinguished one but the section which particularly pleased the reviewer was that concerning the surgical therapy. The author's realistic honest appraisal is refreshing. The book is worthy of being on the desk of every physician who treats any Parkinsonism. S. G.

The Atom Story. BY J. G. FEINBERG, M.Sc. Pp. 243; illustrated. New York: Philosophical Library, Inc., 1954. Price, $4.75.

IN a simple and interesting manner the author has written for the lay reader the story of our knowledge of the atom and its fission, culminating in the newest development, the fusion reaction and the hydrogen bomb. There is a useful appendix on Survival under Atomic Attack, and another on Atomic Tools. R. K.

Wine as Food and Medicine. BY SALVATORE P. LUCIA, A.B., M.D., Sc.D., F.A.C.P., Professor of Medicine, University of California. Pp. 149. New York: The Blakiston Co., 1954. Price, $3.00.

A discussion of wine as a food and as a therapeutic agent, its chemistry, its physiologic and pharmacologic effects, by a physician well versed in his subject whose work will be appreciated by many, in addition to his colleagues, members of The Society of Medical Friends of Wine. R. K.

The Social Psychology of Industry. BY J. A. C. BROWN. Pp. 310. Baltimore: Penguin Books, 1954. Price, $.65.

THE author has brought together in a compact and inexpensive form a very satisfactory survey of old and new psychological trends in the office and factory. The author feels keenly the need to consider not only the individual at work but the social structure which gets him ready for work and in which he lives during and after work. He has chapters on historical retrospect, human nature, the organization of industry as well as chapters on attitude and opinion, surveys, frustration, leaders and leadership.

There are many quotations in the text from able writers in the field and a short bibliography as well. The author claims in his introduction that he wishes to set down some fundamental aspect of human nature and social organization for anyone interested in reorganizing factory life. The book is interestingly written and is highly recommended. O. E.

Donovanosis (Granuloma Inguinale, Granuloma Venereum). BY R. V. RAJAM AND P. N. RANGIAH. Pp. 72; 38 ills. Geneva: World Health Organization, 1954. Price, $1.50.

THIS is the 24th of a series of monographs, sponsored by the World Health Organization. The authors have given a concise, accurate and valuable presentation of the knowledge of this disease, with chapters on history, distribution, etiology, epidemiology, clinical features, diagnosis and treatment. The 38 illustrations are extremely well done. R. K.

Veterans Administration Technical Bulletins, Series 10, Volume VI, 1952 and 1953. Edited by ARTHUR M. WALKER, M.D. Pp. 250. Washington: Veterans Administration, 1954. Not for sale; few copies available to medical libraries.

THIS is the sixth volume of a series of Technical Bulletins issued by the Veterans Administration under the able editorship of Dr. Arthur M. Walker and bringing to the medical officers of the Veterans Administration authoritative and concise statements of clinical problems. The present volume includes seventeen bulletins on a wide range of topics, one of them a reprint of Francis Peabody's classical article on "The Care of the Patient." It is unfortunate that this and the preceding volumes are not for sale. However, they may be obtained by libraries and should prove to be extremely popular reference works. R. K.

Scent Therapy: An Inquiry Into the Possibilities of a Method of Therapy of Psychic Disturbances Through Scent. BY EMERY STERN, PE CE, E E. New York: Psychological Library, 1954. Price, not given.

THE author, in a very brief brochure, gives a few bits of historical information, indicates the capacity for odors to stimulate memories and suggests that it might have psychotherapeutic value. The brief communication is largely an invitation to interested investigators in the area to pursue the subject. O. E.

Good General Practice. BY STEPHEN TAYLOR, M.D., M.R.C.P. Pp. 604; 56 ills. New York: Oxford University Press, 1954. Price, $3.50.

UNDER the auspices of the Nuffield Provincial Hospitals Trust, Dr. Stephen Taylor made an exhaustive survey of general practice under The National Health Service in Britain and he reports his findings and analysis in this volume. There is given a comprehensive picture of general practice from a viewpoint sympathetic to the system but without hesitation to show weaknesses and needs for improvement. There is not space to go into any detail or even a superficial discussion of the material and the conclusions based thereon. But those who are interested in

medical economics and in medical organization should read this book carefully because it contains more objective factual material upon a highly controversial subject than anything that has yet come to this reviewer's attention. Moreover, any general practitioner will find here some excellent ideas and practical suggestions for use in his daily work. R. K.

Eleven Blue Men and Other Narratives of Medical Detection. By BERTON ROUECHE Pp. 215. Boston: Little, Brown & Co., 1954. Price, $3.50.

A reprint of twelve stories of authentic medical detection that first appeared in The New Yorker. They are well done, scientifically correct, and based on fact. Physicians will find them instructive as well as diverting. R. K.

The Hog and I. By CHARIS MILEY. Pp. 93. New York: The Neptune Co., 1954. Price, $1.00.

How one man overcame obesity is recounted in this diverting little volume. Common sense philosophy about nutrition and certain other aspects of daily living are discussed by the author with a prize pure-bred hog. These imaginary conversations occur when the author is rendered unconscious by a fall from a hammock, rebellious against the burden of his corpulence. Persons interested in weight reduction but unable to hew to the mark will enjoy this and profit by its perusal. C. S.

The Concept of Schizophrenia. By W. F. McAULEY, M.D., BELF., D.P.M., R.C.P.S.I., Downshire Hospital, Northern Ireland. Pp. 145. New York: Philosophical Library, 1954. Price, $3.75.

THIS is an up-to-date and fairly inclusive monograph on the disease entity called schizophrenia. It includes an historical perspective as well as a discussion of the theories as to causation and the treatments utilized. More might have been said about current treatment efforts and research perspectives. There is a bibliography and an index. O. E.

The Doctor Writes. Edited by S. O. WAIFE, M. D. Pp. 175; 7 ills. New York: Grune & Stratton, 1954. Price, $3.75.

THIS small volume is an anthology of 17 nontechnical articles which were written by distinguished men of medicine and related sciences. The papers, which had all been published separately before, were collected by the editor, Dr. S. O. Waife, because of their unusual and interesting nature. Several of the contributions are indeed classics of their kind. Among those which may be cited are: "Teachers of Medicine," by W. B. Wood, Jr.; "Creativeness in Medicine," by Alan Gregg; "Trends in Authorship," by Robert Alexander; "Record of the Case," by Sir John Charles; and "Sherlock Holmes as a Dermatologist," by J. V. Klauder.

The editor expressed hope that the contents of this anthology might afford emotional pleasure, intellectual profit, and spiritual peace to the reader. In this reviewer's opinion that hope will be realized. C. Z.

Larvierte Eisenmangelkrankheit. By B. JASINSKI AND O. ROTH. Pp. 206; 33 ills. Basel: Benno Schwabe & Co., 1954 (Intercontinental Medical Book Corporation, New York, U. S. Agents). Price, 19 Swiss fr.

THIS monograph, written in German, deals with iron deficiency diseases. It is divided into two major sections, the first of which is concerned with the physiology and pathophysiology of iron assimilation. The second and larger portion of the work is devoted to the clinical aspects of iron metabolism. Deficiency states in children and in women receive especial consideration. Symptomatology, diagnosis and treatment, including intravenous iron therapy and its indications, are all thoroughly discussed. Clinicians in general, and hematologists in particular, may find much of interest in this volume. C. Z.

The Bacterial Factor in Traumatic Shock. By JACOB FINE, M.D., Department of Surgery, Harvard Medical School. Pp. 71. Springfield, Ill.: Charles C Thomas, 1954. Price, $2.75.

THIS monograph by Doctor Fine outlines the intensive and meticulous laboratory work which he has carried on over the past 10 years. The principal thesis of the monograph deals with the bacterial aspects of shock, particularly the role that they play in creating irreversibility in traumatic shock. The effect of antibiotic therapy by various routes modifying the role of bacteria in shock has been well documented. We consider this to be an outstanding monograph on the subject, and the author's well written descriptions of his laboratory work are most interesting. The book is of particular interest to general surgeons and orthopedists. H. C.

Transactions of the 13th Conference on the Chemotherapy of Tuberculosis, February, 1954. Pp. 442. Washington: Veterans Administration, 1954. Price, not given.

THE present volume contains the proceedings of the 13th Conference on the Chemotherapy of Tuberculosis which was held on February 8 to 11, 1954, in St. Louis, by the Veterans Administration, Army and Navy in cooperation with the National Tuberculosis Association. The reports are grouped under the following headings: Pulmonary Tuberculosis, Meningeal and Miliary Tuberculosis, Laboratory Studies, Surgery in Pulmonary Tuberculosis, "Newer" Drugs in the Treatment of Tuberculosis, Extra-Pulmonary Tuberculosis, and Non-Tuberculous Pulmonary Disease. In addition, there are several sections dealing with administrative matters.

Workers in the field of tuberculosis will find this volume as valuable as the preceding ones of this series. C. Z.

Laboratory Aids in Endocrine Diagnosis. By ROBERTO F. ESCAMILLA, M.D., Assoc. Clin. Professor of Medicine, University of California. Pp. 131; 21 ills., 5 in color. Springfield, Ill.: Charles C Thomas, 1954. Price, $4.75.

IN this small volume, the author has brought together the various tests which may be of help in the diagnosis of endocrine disorders. Each of the respective tests is given in detail and the significance of abnormal values is discussed. Generally, one can agree with the author as to the method chosen and the interpretation offered. In this reviewer's opinion, however, there is insufficient stress placed on the inherent variables of the eosinophile count. Furthermore, the Randolph method for direct counting of eosinophils, which is preferred by many workers, is not mentioned. These deficiencies are relatively minor, however, and the book should be useful to clinicians and medical students alike. C. Z.

Tobacco Dictionary. Edited by RAYMOND JAHN. Pp. 199; 6 ills. New York: Philosophical Library, 1954. Price, $5.00.

THIS small volume not only defines the terms used in connection with tobacco, but it also contains many interesting and curious facts relating to the history, manufacture, and use of tobacco. Physicians will be interested to note that there is included a brief but objective reference to the current discussion on the possible relationship of smoking to cancer of the lung. There is no mention made, however, of possible cardiovascular effects from smoking. C. Z.

Hypertension. Humoral and Neurogenic Factors. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., AND MARGARET P. CAMERON, M.A., A.B.L.S. Pp. 294; 73 ills. Boston: Little, Brown & Co., 1954. Price, $6.75.

THIS volume consists of a series of 21 papers which were presented at a Symposium on "Humoral and Neurogenic Factors in Hypertension," which was held in London in July, 1953, under the auspices of the Ciba Foundation. Contributions were made by a number of outstanding investigators in the field of Hyptertension. In addition, the informal discussions which followed the various papers are included in the printed work.

Anyone interested in the problem of hypertension will find these proceedings both informative and stimulating. C. Z.

Expert Committee on Malaria. Fifth Report. WHO Technical Report Series No. 80. Pp. 42. Geneva: World Health Organization, 1954. Price, $.25.

The Psychological Variables in Human Cancer. Edited by JOSEPH A. GENGERELLI and FRANK J. KIRKNER. Pp. 135. Berkeley and Los Angeles: University of California Press, 1954. Price, $3.00.

THIS is a symposium report by physicians and psychologists who are searching for clues to the possible emotional factors in the production of cancer or those factors which weigh or alter in some way the course of malignant neoplastic disease in humans. There is a section on the possibilities of psychosomatic influence and a discussion of the psychological approach. Test results are given along with case summaries and psychological profiles. A thought-provoking study by capable people on one of our, as yet unsolved, complex medical problems. O. E.

The Microphysical World. By WILLIAM WILSON, PH.D. (LEIPZIG) D.SC. (LONDON), F.R.S. Fellow of King's College, London, and Professor Emeritus of Physics in the University of London. Pp. 216; 23 ills. New York: Philosophical Library, Inc., 1954. Price, $3.75.

THIS book gives an excellent account of the structure of atoms and of their behavior. It deals with phenomena such as heat, light, Roentgen-rays, magnetic effects, quantum theory, radioactivity which can be traced back to molecules, atoms, and the subatomic particles. The way in which this knowledge has been acquired is explained in simple language and the text is not broken with mathematical formulae.

The author skillfully portrays developments from the earliest knowledge of microphysical phenomena to the modern quantum theory, from Dalton's atom to inside the nucleus. G. H.

The Retinal Circulation in Man and Animals. By I. C. MICHAELSON, PH.D. (GLAS.), F.R.F.P.S. (GLAS.), D.O.M.S. (ENG.), Chief of Department of Ophthalmology, The Government Hospital, Haifa. Pp. 131; 95 ills. Springfield, Ill.: Charles C Thomas, 1954. Price, $6.75.

THIS brief book about a rather limited subject is well-written. It is based on adequate experimental material. It is of value to those who are doing research on this circulation. The practical application of this time-consuming effort are rather limited. G. G.

The Third Revolution. By KARL STERN. Pp. 306. New York: Harcourt, Brace & Co., 1954. Price, $4.00.

THIS is a book on the subject of the relation of psychiatry to religion. The title alludes to the two preceding revolutions which gave so

much importance to biology through racism. Stern argues that the basic concepts of psychoanalysis are compatible with the Christian idea but that we must at the same time try to avoid reducing the spiritual too far in the direction of the material, else we threaten to destroy the unique nature of man. O. E.

Rheumatic Fever. By LOWELL A. RANTZ, M.D. DM (Disease-a-Month), October, 1954. Pp. 35. Chicago: The Year Book Publishers, Inc., 1954. Price, $9.00 per annum.

THIS is an interesting monograph on the submonograph which covers all aspects of rheumatic fever including discussions of etiology, epidemiology, natural history, prognosis and treatment. This should be particularly well worth while for the medical student and the busy practitioner. G. M.

Roberta Cowell's Story. By ROBERTA COWELL. Pp. 208; 20 ills. New York: British Book Centre, Inc., 1954. Price, $3.00.

THIS is the autobiography of a man who lived a masculine existence until middle life and then through surgical, hormonal, and psychological therapy changed into a woman. He had seen war experience, been married and fathered two children, but due to gradual physical and psychological changes decided to avail himself of all possible medical help to make a complete change. The book is a personal narrative account and there are no documented scientific observations, hence is probably of more interest to the lay than the medical world. O. E.

Hypothyroidism. By PAUL STARR, M.D., Professor of Medicine, University of Southern California. Pp. 127; 25 ills. Springfield, Ill.: Charles C Thomas, 1954. Price, $3.75.

THIS is an interesting monograh on the subject of hypothyroidism. It covers the etiology, classification and diagnosis as well as the clinical syndromes and methods of therapy. Although the major aspects of this presentation are well known and accepted, certain new considerations are presented many of which are still in the theoretical realm. Of particular interest is the author's division of hypothyroid etiology into four aspects: that due to primary thyroid deficiency, that due to hypofunction of the pituitary, a third type resulting from hypothalamic disturbances and finally, a type of hypothyroidism due to lack of normal peripheral utilization. W. P.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

Published Monthly. Illustrated.

Subscription price: 1 year $10.00; 2 years $18.00.
(One year subscription to Canada, South and Central America, Philippines and Spain, $10.36; all other countries $11.14.)

All foreign subscriptions payable in advance in United States dollars.

Business Correspondence: Lea & Febiger, 600 S. Washington Sq., Philadelphia 6, Pa.

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